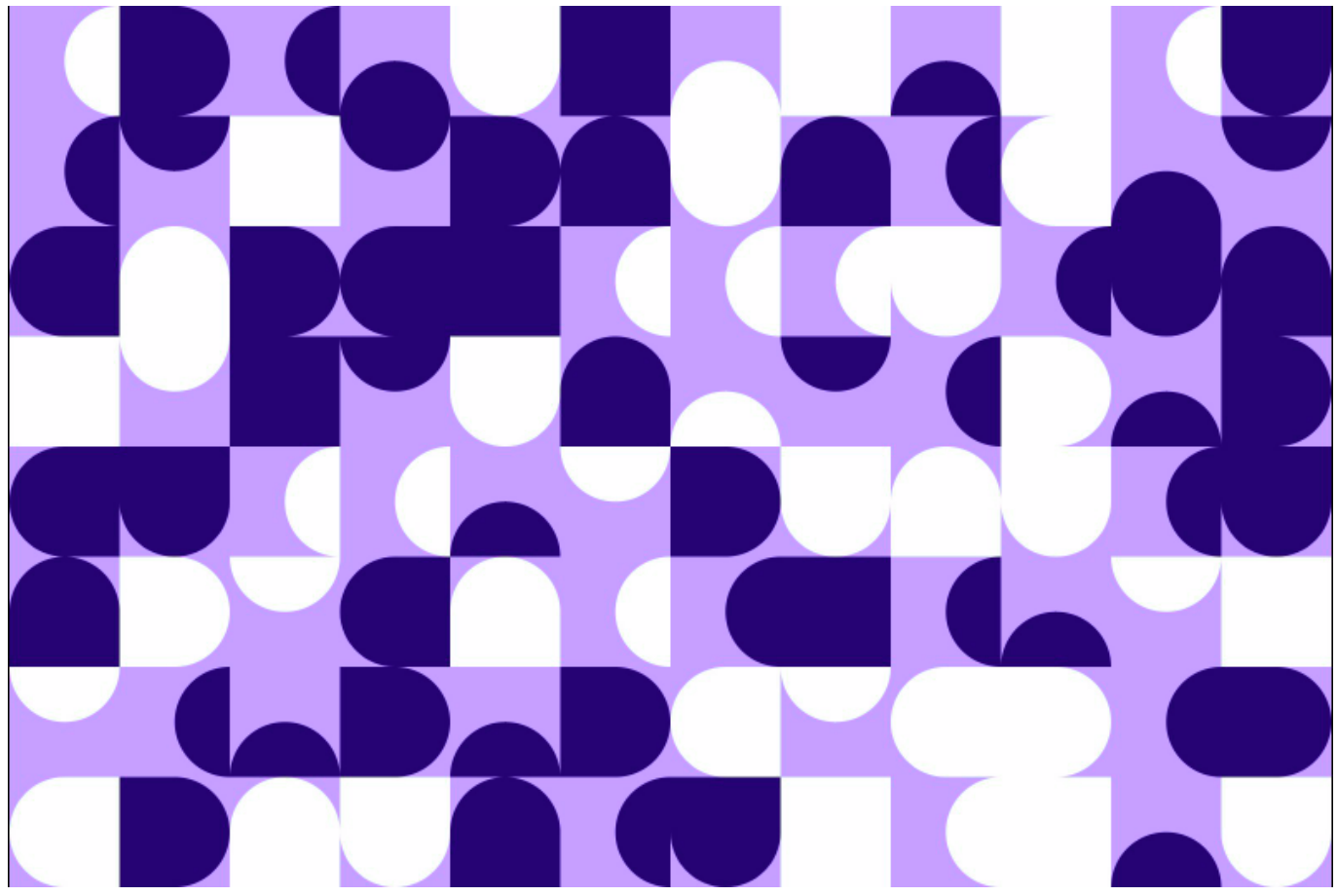

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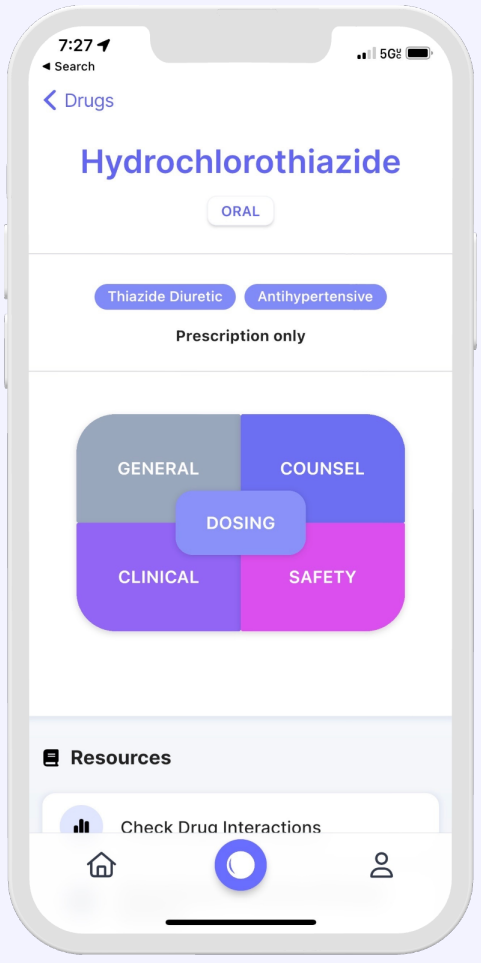

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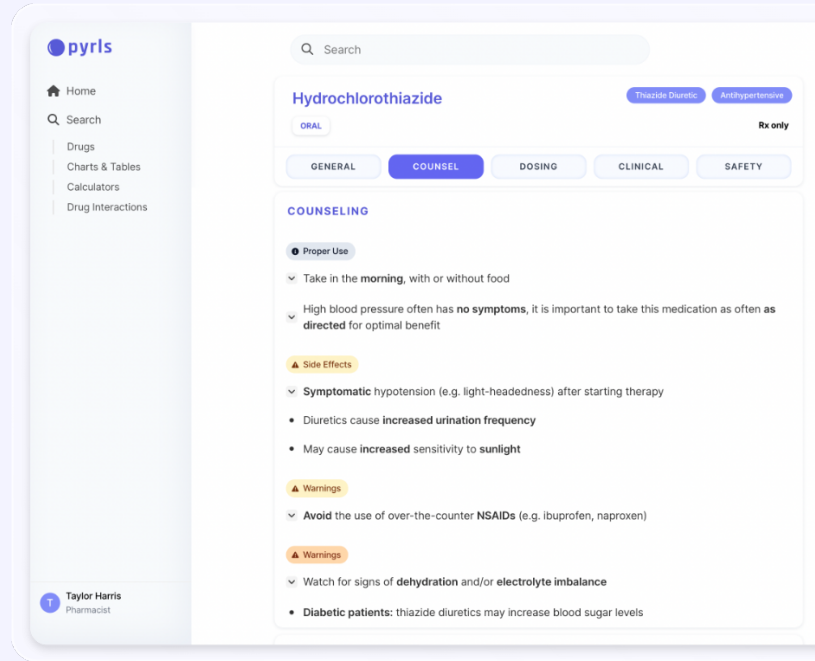

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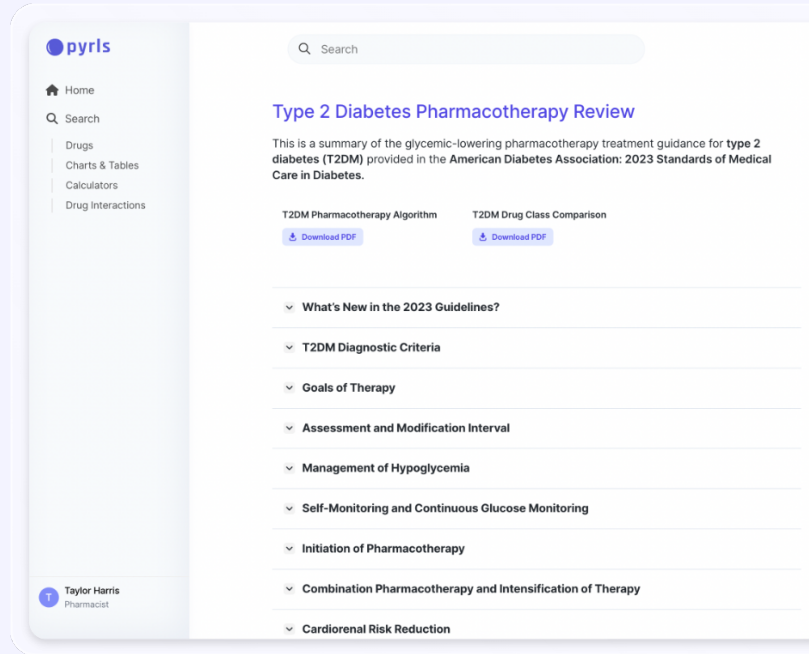

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Table of Contents

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Asthma Management in Ages 12+ Years

Based on the 2023 Global Initiative for Asthma (GINA) Report

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Asthma management is an individualized, continuous cycle of assessment, treatment/adjustment, and review

Assess
- Confirm or evaluate diagnosis, if necessary
- Symptom control & modifiable risk factors
- Comorbidities
- Patient goals & inhaler technique/adherence

Adjust
- Treat comorbidities, & modifiable risk factors
- Utilize non-pharmacotherapy, if possible
- Add/adjust asthma medications
- Educate and train skills and proper use

Review
- Symptoms, lung function
- Asthma exacerbations
- Medication/treatment side effects
- Patient satisfaction, quality of life

Repeat
- Assess
- Adjust
- Review

TRACK 1 Preferred Approach

- **Reliever:** As-needed low dose ICS-formoterol
- **Controller:** Follow steps

	START HERE IF:	START HERE IF:	START HERE IF:	
	Symptoms < 4-5 days/week	Symptoms most days or waking with asthma ≥ 1 time/week	Daily symptoms or waking with asthma ≥ 1 time/week and low lung function	← A short course of OCS may be needed in those presenting with severe, uncontrolled asthma
Controller →	**Step 1 & Step 2** **As-needed only low dose ICS-formoterol**	**Step 3** **Low dose maintenance ICS-formoterol (MART)**	**Step 4** **Medium dose maintenance ICS-formoterol (MART)**	**Step 5** **Add on LAMA** **Refer for phenotypic assessment with or without biologic therapy** **Consider high dose ICS-formoterol (MART)**
Reliever →	**Reliever:** As-needed low dose ICS-formoterol			

The alternate approach is reasonable when: preferred approach is not possible, if patient is stable on their current therapy (e.g., no exacerbation within the past year), or alternate approach is preferred by the patient

TRACK 2 Alternate Approach

- **Reliever:** As-needed SABA or as-needed ICS-SABA
- **Controller:** Follow steps

	START HERE IF:	START HERE IF:	START HERE IF:	START HERE IF:	
	Symptoms < 2 times/month	Symptoms ≥ 2/month but < 4-5 days/week	Symptoms most days or waking with asthma ≥ 1 time/week	Daily symptoms or waking with asthma ≥ 1 time/week and low lung function	← A short course of OCS may be needed in those presenting with severe, uncontrolled asthma
Controller →	**Step 1** **Take ICS whenever SABA is taken**	**Step 2** **Low dose maintenance ICS**	**Step 3** **Low dose maintenance ICS-LABA**	**Step 4** **Medium/high dose maintenance ICS-LABA**	**Step 5** **Add on LAMA** **Refer for phenotypic assessment with or without biologic therapy** **Consider high dose ICS-LABA**
Reliever →	**Reliever:** As-needed short-acting β2-agonist (SABA)* or as-needed ICS-SABA				

*If considering SABA reliever, confirm that the patient is likely to be adherent to daily controller treatment

Other Controller Options for use in either approach

Other Controller → Options	Step 1	Step 2	Step 3	Step 4	Step 5
		Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	Medium dose ICS, or add LTRA, or add HDM SLIT	Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS	Add azithromycin (for adults) or LTRA; add low dose OCS as last resort

HDM: house dust mite; **ICS:** inhaled corticosteroid; **LABA:** long-acting beta-2 agonist; **LAMA:** long-acting muscarinic antagonist; **LTRA:** leukotriene receptor antagonist; **MART:** maintenance and reliever therapy; **OCS:** oral corticosteroids; **SABA:** short-acting beta-2 agonist; **SLIT:** sublingual immunotherapy

Asthma Management in Ages 11 Years and Under

Based on the 2023 Global Initiative for Asthma (GINA) Report

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Asthma management is an individualized, continuous cycle of assessment, treatment/adjustment, and review

Assess
- Confirm or evaluate diagnosis, if necessary
- Symptom control & modifiable risk factors
- Comorbidities
- Patient goals & inhaler technique/adherence

Adjust
- Treat comorbidities, & modifiable risk factors
- Utilize non-pharmacotherapy, if possible
- Add/adjust asthma medications
- Educate and train skills and proper use

Review
- Symptoms, lung function
- Asthma exacerbations
- Medication/treatment side effects
- Patient satisfaction, quality of life

Repeat
- Assess
- Adjust
- Review

Children ages 6-11 years

- **Reliever:** As-needed SABA or low dose ICS-formoterol for MART (Steps 3-4)
- **Controller:** Follow steps

← A short course of OCS may be needed in those presenting with severe, uncontrolled asthma

	Step 1	Step 2	Step 3	Step 4	Step 5
	START HERE IF: Symptoms < 2 times/month	**START HERE IF:** Symptoms ≥ 2 times/month but less than daily	**START HERE IF:** Symptoms most days or waking with asthma ≥ 1 time/week	**START HERE IF:** Symptoms most days or waking with asthma ≥ 1 time/week and low lung function	
Preferred Controller →	**Take low dose ICS whenever SABA is taken**	**Daily low dose ICS** (use child dose ranges)	**Low dose ICS-LABA, or medium dose ICS, or very low dose ICS-formoterol as maintenance & reliever therapy (MART)**	**Medium dose ICS-LABA, or low dose ICS-formoterol as maintenance & reliever therapy (MART)** **Refer for expert advice**	**Refer for phenotypic assessment** **Consider higher dose ICS-LABA or add-on therapy (e.g., anti-IgE, anti-IL4R, anti-IL5)**
Other Controller → Options	Consider daily low dose ICS	Daily LTRA, or low dose ICS whenever SABA is taken	Low dose ICS + LTRA	Add tiotropium or add LTRA	Consider add-on low dose OCS (last resort)
Reliever →	**Reliever:** As-needed short-acting β2-agonist (SABA) or ICS-formoterol for MART as above in Steps **3 & 4**				

Children ages 5 years and younger

- **Reliever:** As-needed SABA
- **Controller:** Follow steps

Before stepping up, check for alternate diagnosis, confirm proper inhaler use, review adherence & exposures

	Step 1	Step 2	Step 3	Step 4
	CONSIDER THIS STEP IF: Infrequent viral wheezing & no or few interval symptoms	**CONSIDER THIS STEP IF:** Symptoms are not consistent with asthma, but wheezing episodes requiring SABA occur frequently (e.g., ≥ 3/year). Give a 3-month diagnostic trial. Consider expert referral. or Symptoms are consistent with asthma and are not well controlled or ≥ 3 exacerbations per year.	**CONSIDER THIS STEP IF:** Confirmed asthma & not well-controlled on low dose ICS	**CONSIDER THIS STEP IF:** Asthma not well controlled on doubled dose of initial low dose ICS
Preferred Controller →	*Not enough evidence for daily controller*	**Daily low dose ICS** (use ages 5 years and under low ICS dose range approximations)	**Double the initial low-dose ICS**	**Continue controller** **Refer for specialist assessment**
Other Controller → Options	Consider intermittent short ICS course at onset of viral illness	Daily LTRA, or intermittent short courses of ICS at onset of respiratory illness	Low dose ICS + LTRA; Consider specialist referral	Add LTRA, or add intermittent ICS, or increase ICS frequency
Reliever →	**Reliever:** As-needed short-acting β2-agonist (SABA)			

ICS: inhaled corticosteroid; **LABA:** long-acting beta-2 agonist; **LAMA:** long-acting muscarinic antagonist; **LTRA:** leukotriene receptor antagonist; **MART:** maintenance and reliever therapy; **OCS:** oral corticosteroids; **SABA:** short-acting beta-2 agonist

SABA
SHORT-ACTING BETA-2 AGONIST

ProAir HFA Ⓖ — 4+
METERED DOSE (200 inhalations)
Albuterol

ProAir Respiclick — 4+
DRY POWDER (200 inhalations)
Albuterol

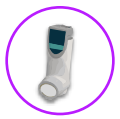
ProAir Digihaler — 4+
DRY POWDER (200 inhalations)
Albuterol

Proventil HFA Ⓖ — 4+
METERED DOSE (200 inhalations)
Albuterol

Ventolin HFA Ⓖ — 4+
METERED DOSE (200 inhalations)
Albuterol

Xopenex HFA Ⓖ — 4+
METERED DOSE (200 inhalations)
Levalbuterol

SABA + ICS
COMBINATION



Airsupra — 18+
METERED DOSE (120 inhalations)
Albuterol/Budesonide

SAMA
SHORT-ACTING MUSCARINIC ANTAGONIST

Atrovent HFA — C
METERED DOSE (200 inhalations)
Ipratropium

SAMA + SABA
COMBINATION

Combivent Respimat — C
SOFT MIST (120 inhalations)
Ipratropium/Albuterol

LABA
LONG-ACTING BETA-2 AGONIST

Serevent Diskus — 4+ 4+ C
DRY POWDER (60 inhalations)
Salmeterol

Striverdi Respimat — C
SOFT MIST (60 inhalations)
Olodaterol

LAMA
LONG-ACTING MUSCARINIC ANTAGONIST

Incruse Ellipta — C
DRY POWDER (30 inhalations)
Umeclidinium

Spiriva Handihaler — C
DRY POWDER (30 doses [2 inhalations/capsule])
Tiotropium

Spiriva Respimat — 6+ C
SOFT MIST (60 inhalations)
Tiotropium

Tudorza Pressair — C
DRY POWDER (60 inhalations)
Aclidinium

LAMA + LABA
COMBINATION

Anoro Ellipta — C
DRY POWDER (30 inhalations)
Umeclidinium/Vilanterol

Bevespi Aerosphere — C
METERED DOSE (120 inhalations)
Glycopyrrolate/Formoterol

Duaklir Pressair — C
DRY POWDER (60 inhalations)
Aclidinium/Formoterol

Stiolto Respimat — C
SOFT MIST (60 inhalations)
Tiotropium/Olodaterol

ICS + LAMA + LABA
COMBINATION

Breztri Aerosphere — C
METERED DOSE (120 inhalations)
Budesonide/Glycopyrrolate/Formoterol

Trelegy Ellipta — 18+ C
DRY POWDER (30 inhalations)
Fluticasone furoate/Umeclidinium/Vilanterol

ICS
INHALED CORTICOSTEROID

Alvesco — 12+
METERED DOSE (60 inhalations)
Ciclesonide

ArmonAir Digihaler — 12+
DRY POWDER (60 inhalations)
Fluticasone propionate

Arnuity Ellipta — 5+
DRY POWDER (30 inhalations)
Fluticasone furoate

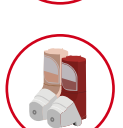
Asmanex Twisthaler — 4+
DRY POWDER (110 mcg: 30 inhalations)
(220 mcg: 120 inhalations)
Mometasone

Asmanex HFA — 5+
METERED DOSE (120 inhalations)
Mometasone

Flovent Diskus *Brand discontinued; Authorized generic available* — 4+
DRY POWDER (60 inhalations)
Fluticasone propionate

Flovent HFA *Brand discontinued; Authorized generic available* — 4+
METERED DOSE (120 inhalations)
Fluticasone propionate

Pulmicort Flexhaler — 6+
DRY POWDER (90 mcg: 60 inhalations)
(180 mcg: 120 inhalations)
Budesonide



QVAR RediHaler — 4+
METERED DOSE (120 inhalations)
Beclomethasone

ICS + LABA
COMBINATION

Advair Diskus Ⓖ — 4+ C
DRY POWDER (60 inhalations)
Fluticasone prop./Salmeterol

Advair HFA Ⓖ — 12+
METERED DOSE (120 inhalations)
Fluticasone prop./Salmeterol

AirDuo RespiClick Ⓖ — 12+
DRY POWDER (60 inhalations)
Fluticasone prop./Salmeterol

AirDuo Digihaler — 12+
DRY POWDER (60 inhalations)
Fluticasone prop./Salmeterol

Breo Ellipta — 5+ C
DRY POWDER (30 inhalations)
Fluticasone furoate/Vilanterol

Breyna *Generic for Symbicort* — 6+ C
METERED DOSE (120 inhalations)
Budesonide/Formoterol

Dulera — 5+
METERED DOSE (120 inhalations)
Mometasone/Formoterol

Symbicort Ⓖ — 6+ C
METERED DOSE (120 inhalations)
Budesonide/Formoterol

Wixela Inhub *Generic for Advair Diskus* — 4+ C
DRY POWDER (60 inhalations)
Fluticasone prop./Salmeterol

FDA-APPROVED INDICATIONS* # = Age (years) approved for asthma # = Age (years) approved for bronchospasms C = Approved for COPD

Updated 1/2024

**SABAs are FDA-approved for bronchospasms in reversible obstructive airway diseases and exercised-induced bronchospasm (EIB), except Xopenex (levalbuterol) is not indicated for EIB; Airsupra (albuterol/budesonide) is indicated as-needed for bronchoconstriction and to reduce the risk of exacerbations in asthma; Serevent Diskus (salmeterol) is indicated for EIB, asthma (in addition to an ICS), and COPD. Indications and evidence for individual agents are subject to change and geographic variability.*

Ⓖ Authorized generic available

Ⓖ Both authorized generic and branded generic available

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FDA-APPROVED INDICATIONS* # = Age (years) approved for asthma # = Age (years) approved for bronchospasms C = Approved for COPD **Updated 12/2023**

**SABAs are FDA-approved for bronchospasms in reversible obstructive airway diseases and exercised-induced bronchospasm (EIB), except Xopenex (levalbuterol), which is not indicated for EIB; Airsupra (albuterol/budesonide) is indicated as-needed for bronchoconstriction and to reduce the risk of exacerbations in asthma; Serevent Diskus (salmeterol) is indicated for EIB, asthma (in addition to an ICS), and COPD. Indications and evidence are subject to change and geographic variability.*

Aclidinium
Long-Acting Muscarinic Antagonist
TUDORZA PRESSAIR™ C
400 mcg

Aclidinium/Formoterol
Long-Acting Muscarinic Antagonist/
Long-Acting Beta-2 Agonist
DUAKLIR PRESSAIR® C
400/12 mcg

Albuterol
Short-Acting Beta-2 Agonist
PROAIR®, PROVENTIL®, VENTOLIN® 4+
90 mcg
Authorized generics available

Albuterol/Budesonide
Short-Acting Beta-2 Agonist/
Inhaled Corticosteroid
AIRSUPRA™ 18+
90/80 mcg

Beclomethasone
Inhaled Corticosteroid
QVAR REDIHALER® 4+
40, 80 mcg

Budesonide
Inhaled Corticosteroid
PULMICORT FLEXHALER® 6+
90, 180 mcg

Budesonide/Formoterol
Inhaled Corticosteroid/
Long-Acting Beta-2 Agonist
SYMBICORT® 6+ C
80/4.5, 160/4.5 mcg
Generics: Both an authorized generic and Breyna available

Budesonide/Glycopyrrolate/Formoterol
Inhaled Corticosteroid/
Long-Acting Muscarinic Antagonist/Long-Acting Beta-2 Agonist
BREZTRI AEROSPHERE™ C
160/9/4.8 mcg

Ciclesonide
Inhaled Corticosteroid
ALVESCO® 12+
80, 160 mcg

Fluticasone furoate
Inhaled Corticosteroid
ARNUITY ELLIPTA® 5+
50, 100, 200 mcg

Fluticasone propionate
Inhaled Corticosteroid
ARMONAIR DIGIHALER® 12+
55, 113, 232 mcg
FLOVENT DISKUS® 4+
50, 100, 250 mcg
FLOVENT® HFA 4+
44, 110, 220 mcg
Flovent products are not available; Only their authorized generics are available

Fluticasone/Salmeterol
Inhaled Corticosteroid/
Long-Acting Beta-2 Agonist
AIRDUO® [RespiClick/Digihaler] 12+
55/14, 113/14, 232/14 mcg
ADVAIR DISKUS® 4+ C
100/50, 250/50, 500/50 mcg
ADVAIR® HFA 12+
45/21, 115/21, 230/21 mcg
Advair HFA, AirDuo: Authorized generics available
Advair Diskus: Both an authorized generic and Wixela Inhub available

Fluticasone/Umeclidinium/Vilanterol
Inhaled Corticosteroid/
Long-Acting Muscarinic Antagonist/Long-Acting Beta-2 Agonist
TRELEGY ELLIPTA® 18+ C
100/62.5/25 mcg
200/62.5/25 mcg

Fluticasone/Vilanterol
Inhaled Corticosteroid/
Long-Acting Beta-2 Agonist
BREO ELLIPTA® 5+ C
50/25, 100/25, 200/25 mcg

Glycopyrrolate/Formoterol
Long-Acting Muscarinic Antagonist/
Long-Acting Beta-2 Agonist
BEVESPI AEROSPHERE® C
9/4.8 mcg

Ipratropium
Short-Acting Muscarinic Antagonist
ATROVENT® HFA C
~17 mcg

Ipratropium/Albuterol
Short-Acting Muscarinic Antagonist/
Short-Acting Beta-2 Agonist
COMBIVENT RESPIMAT® C
20/100 mcg

Levalbuterol
Short-Acting Beta-2 Agonist
Xopenex® 4+
45 mcg
Authorized generic available

Mometasone
Inhaled Corticosteroid
ASMANEX TWISTHALER® 4+
110, 220 mcg
ASMANEX® HFA 5+
50, 100, 200 mcg

Mometasone/Formoterol
Inhaled Corticosteroid/
Long-Acting Beta-2 Agonist
DULERA® 5+
50/5, 100/5, 200/5 mcg

Olodaterol
Long-Acting Beta-2 Agonist
STRIVERDI RESPIMAT® C
2.5 mcg

Salmeterol
Long-Acting Beta-2 Agonist
SEREVENT DISKUS® 4+ 4+ C
50 mcg

Tiotropium
Long-Acting Muscarinic Antagonist
SPIRIVA HANDIHALER® C
18 mcg
SPIRIVA RESPIMAT® 6+ C
1.25, 2.5 mcg

Tiotropium/Olodaterol
Long-Acting Muscarinic Antagonist/
Long-Acting Beta-2 Agonist
STIOLTO RESPIMAT® C
2.5/2.5 mcg

Umeclidinium
Long-Acting Muscarinic Antagonist
INCRUSE ELLIPTA® C
62.5 mcg

Umeclidinium/Vilanterol
Long-Acting Muscarinic Antagonist/
Long-Acting Beta-2 Agonist
ANORO ELLIPTA® C
62.5/25 mcg

ICS DAILY DOSE CATEGORIZATION
IN ADULTS AND CHILDREN AGE 6 YEARS AND UP

ICS (DELIVERY)	TOTAL DAILY DOSE (MCG/DAY)			
	Age	Low	Medium	High
Beclomethasone (MDI)	12+ years	100-200	>200-400	>400
	6-11 years	50-100	>100-200	>200
Budesonide (DPI)	12+ years	200-400	>400-800	>800
	6-11 years	100-200	>200-400	>400
Ciclesonide (MDI)	12+ years	80-160	>160-320	>320
	6-11 years	80	>80-160	>160
Fluticasone furoate (DPI)	12+ years	100	100	200
	6-11 years	50	50	N/A
Fluticasone prop. (DPI)	12+ years	100-250	>250-500	>500
	6-11 years	50-100	>100-200	>200
Fluticasone prop. (MDI)	12+ years	100-250	>250-500	>500
	6-11 years	50-100	>100-200	>200
Mometasone (DPI)	12+ years	200	200	400
	6-11 years	N/A	N/A	N/A
Mometasone (MDI)	12+ years	200-400	200-400	>400
	6-11 years	100	100	200

ICS DAILY LOW DOSE CATEGORIZATION
IN CHILDREN AGE 5 YEARS AND YOUNGER

ICS (DELIVERY)	LOW TOTAL DAILY DOSE (MCG/DAY) (Age group with adequate safety & efficacy data)
Beclomethasone (MDI)	**50** (ages 5+ years)
Budesonide (nebulized)	**500** (ages 1+ years)
Ciclesonide (MDI)	**Not sufficiently studied in age 5 and under**
Fluticasone furoate (DPI)	**50** (ages 5+ years)
Fluticasone prop. (MDI)	**50** (ages 4+ years)
Mometasone (MDI)	**100** (ages 5+ years)

References: 2023 GINA Report: Global Strategy for Asthma Management and Prevention, FDA Prescribing Information for the individual medications.

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ICS-Containing Inhaler Estimated Dose Categorizations

Adults and Adolescents 12 Years and Older

ICS Inhaler Estimated Dose Categories in Adults and Adolescents 12 Years and Older

Age 12+ | Age 12+

	Alvesco	Arnuity Ellipta	Asmanex HFA	Asmanex Twisthaler	Flovent Diskus	Flovent HFA	Pulmicort Flexhaler	QVAR RediHaler
Generic	Ciclesonide	Fluticasone furoate	Mometasone	Mometasone	Fluticasone prop.	Fluticasone prop.	Budesonide	Beclomethasone
Delivery	METERED DOSE	DRY POWDER	METERED DOSE	DRY POWDER	DRY POWDER	METERED DOSE	DRY POWDER	METERED DOSE
Indication	A Asthma: 12+ yrs	A Asthma: 5+ yrs	A Asthma: 5+ yrs	A Asthma: 4+ yrs	A Asthma: 4+ yrs	A Asthma: 4+ yrs	A Asthma: 6+ yrs	A Asthma: 4+ yrs
Available Product Strengths	80 mcg/inh; 160 mcg/inh	50 mcg/inh; 100 mcg/inh; 200 mcg/inh	50 mcg/inh; 100 mcg/inh; 200 mcg/inh	110 mcg/inh; 220 mcg/inh	50 mcg/inh; 100 mcg/inh; 250 mcg/inh	44 mcg/inh; 110 mcg/inh; 220 mcg/inh	90 mcg/inh; 180 mcg/inh	40 mcg/inh; 80 mcg/inh
Low Dose†	1 puff BID	1 inh. QD; 1 inh. QD	1 puff* BID	1 inh. QD	1 inh. BID	2 puffs BID; 1 puff BID	1-2 inh. BID; 1 inh. BID	1-2 puffs BID; 1 puff BID
Medium Dose†	1 puff BID	1 inh. QD	2 puffs BID; 1 puff* BID	2 inh. QD or 1 inh. BID	2 inh. BID; 1 inh. BID	2 puffs BID; 1 puff BID	2 inh. BID	2 puffs BID
High Dose†	2 puffs BID	1 inh. QD	2 puffs BID	2 inh. BID	2-4 inh. BID	2-4 puffs BID	3-4 inh. BID	3-4 puffs BID

ICS/LABA and ICS/LAMA/LABA Inhaler Estimated Dose Categories in Adults and Adolescents 12 Years and Older

Age 12+ | Age 12+

	Breo Ellipta	Dulera	Advair Diskus	Advair HFA	AirDuo RespiClick	Symbicort	Breztri Aerosphere	Trelegy Ellipta
Generic	Fluticasone fur./ Vilanterol	Mometasone/ Formoterol	Fluticasone prop./ Salmeterol	Fluticasone prop./ Salmeterol	Fluticasone prop./ Salmeterol	Budesonide/ Formoterol	Budesonide/ Glycopyrrolate/ Formoterol	Fluticasone fur./ Umeclidinium/ Vilanterol
Delivery	DRY POWDER	METERED DOSE	DRY POWDER	METERED DOSE	DRY POWDER	METERED DOSE	METERED DOSE	DRY POWDER
Indication	A Asthma: 5+ yrs C COPD	A Asthma: 5+ years	A Asthma: 4+ years C COPD	A Asthma: 12+ years	A Asthma: 12+ years	A Asthma: 6+ years C COPD	C COPD	A Asthma: 18+ yrs C COPD
Available Product Strengths	50/25 mcg/inh; 100/25 mcg/inh; 200/25 mcg/inh	50/5 mcg/inh; 100/5 mcg/inh; 200/5 mcg/inh	100/50 mcg/inh; 250/50 mcg/inh; 500/50 mcg/inh	45/21 mcg/inh; 115/21 mcg/inh; 230/21 mcg/inh	55/14 mcg/inh; 113/14 mcg/inh; 232/14 mcg/inh	80/4.5 mcg/inh; 160/4.5 mcg/inh	160/9/4.8 mcg/inh	100/62.5/25 mcg/inh; 200/62.5/25 mcg/inh
Low Dose†	1 inh. QD	1*-2 puffs BID	1 inh. BID	2 puffs BID; 1 puff* BID	1 inh. BID; 1 inh. BID	2 puffs BID; 1 puff* BID	1 puff* BID	1 inh. QD
Medium Dose†	1 inh. QD	1 puff* BID	1 inh. BID	2 puffs BID; 1 puff* BID	1 inh. BID	2 puffs BID	2 puffs BID	1 inh. QD
High Dose†	1 inh. QD	2 puffs BID	1 inh. BID	2 puffs BID	1 inh. BID	2 puffs BID	2 puffs BID	1 inh. QD

Notes

The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The definitions of "low", "medium", and "high" dose ICS may vary by source. Where applicable, this resource reflects updated guidance from GINA 2023 which contains more conservative dose recommendations for these categories than previous GINA reports and NHLBI EPR-3 based upon recognition that generally the most benefit is obtained with the low dose; however, ICS response varies by the individual. **References:** NHLBI EPR 2007 and 2020 Focused Updates to the Asthma Management Guidelines, 2023 GINA Report: Global Strategy for Asthma Management and Prevention, manufacturer product information.

***Off-label dosing regimen**

† View manufacturer product information regarding disease-specific dosing and titration

Published January 2024

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Children Age 5-11

ICS Inhaler Estimated Dose Categories in Children Age 5-11 Years

Children Age 5-11

✨ **Ages 5-11 Chart included with Pyrls Pro!**

Type 2 Diabetes Drug Class Comparison

T2DM Drug Class	Mechanism	Route	A1C Lowering*	Hypoglycemia Risk	Weight Effect*	Cost
Biguanides (metformin)	Decreases hepatic production of glucose; increases insulin sensitivity	Oral	●●●	No	Potential for weight loss	$
SGLT2 inhibitors	Increases urinary glucose excretion	Oral	●●	No	Weight loss	$$$
GLP-1 receptor agonists	Increases glucose-dependent insulin release; decreases glucagon secretion; slows gastric emptying	SQ/Oral	●●●●**	No	Weight loss**	$$$$
GLP-1/GIP receptor agonists (e.g. tirzepatide)	Increases glucose-dependent insulin release; decreases glucagon secretion; slows gastric emptying	SQ	●●●●●	No	Weight loss	$$$$$
DPP-4 inhibitors	Increases glucose-dependent insulin release; decreases glucagon secretion	Oral	●	No	Neutral	$$$
Thiazolidinediones	Increases insulin sensitivity in muscle, fat and liver cells; increases glucose entry into cells	Oral	●●	No	+ Weight gain	$^
Sulfonylureas	Stimulates insulin secretion from pancreatic beta cells	Oral	●●●	Yes	+ Weight gain	$
Insulin Analogs	Stimulates peripheral glucose uptake by skeletal muscle and fat tissue; inhibits hepatic glucose production	SQ	●●●●● Titrate to response	Yes	+++ Weight gain	$$$
Human Insulin		SQ/Inhaled				$

SQ = subcutaneous

* The extent of A1C lowering and weight change is highly variable based upon factors including but not limited to baseline A1C, baseline weight, patient-specific characteristics, lifestyle modifications, and whether monotherapy or a multi-drug regimen is being utilized.

** The GLP-1 receptor agonists dulaglutide and subcutaneous semaglutide have notably greater A1C-lowering efficacy and weight loss effects than other GLP-1 receptor agonists.

^ Pioglitazone is generic and has low cost; however, rosiglitazone (Avandia®), which is currently unavailable in the U.S., is not available as a generic.

References: (1) American Diabetes Association Professional Practice Committee. American Diabetes Association. Standards of Care in Diabetes - 2024. Diabetes Care 1 January 2024; 47 (Suppl. 1): S1–S321. (2) Individual manufacturer product labels.

Type 2 Diabetes Pharmacotherapy

Treatment Algorithm for Glycemic Control (2024 Update)

References: American Diabetes Association Professional Practice Committee. American Diabetes Association. Standards of Care in Diabetes - 2024. Diabetes Care 1 January 2024; 47 (Suppl. 1): S1–S321. Individual FDA Prescribing Information labels.

Page 1

Healthy lifestyle behaviors, self-management education/support and social determinants of health should be considered in all patients.

First-line pharmacotherapy (metformin or other agents) should be selected based upon patient-specific factors *(e.g., glycemic goals, cardiorenal risk, comorbidities, cost and access)*.

Consider **combination pharmacotherapy** at initiation if A1C ≥1.5% above target goal.

Consider **early insulin initiation** with extreme hyperglycemia:
- BG ≥300 mg/dL
- A1C >10%
- Signs of catabolism

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Reassess treatment plan every **3-6 months** and modify if appropriate

Glycemic Treatment Goals

Treatment goals must be individualized (and periodically reassessed) after taking into consideration comorbid conditions, hypoglycemia risk, and other patient-specific characteristics.

POPULATION	A1C (%)	PREPRANDIAL	2-HR PPG
Most patients*	<7.0	80 - 130 mg/dL	<180 mg/dL
Certain patients**	<8.0	- -	- -

*More strict goals may be reasonable for certain patients, if achievable without significant hypoglycemia risk
**Risk of severe hypoglycemia, limited life expectancy, long duration of DM, prefer a less stringent A1C goal, etc.

Established/High-Risk of ASCVD, Heart Failure, or Chronic Kidney Disease? No

Recommended independent of baseline A1C, target A1C goal, or use of metformin

ASCVD
(established or high risk^)

GLP-1 RA or SGLT2i with proven CVD benefit

If A1C above target
- On GLP-1 RA? Consider use of SGLT2i with CVD benefit *(and vice versa)*
- Consider low dose TZD *(avoid in patients with HF)*

Heart Failure
(preserved or reduced EF)

SGLT2i† with HF benefit
- Avoid TZDs
- Avoid saxagliptin

If A1C above target

Chronic Kidney Disease
(eGFR < 60 mL/min and/or UACR ≥ 30 mg/g)

On maximally tolerated **ACEi/ARB**

SGLT2i with primary evidence for reducing CKD progression
- May be initiated with an eGFR as low as 20 mL/min
- Strongest evidence of benefit when UACR ≥ 200 mg/g
- If SGLT2i therapy is contraindicated or not tolerated, use of a **GLP-1 RA** with CVD benefit is recommended

If A1C above target

On SGLT2i? Consider use of GLP-1 RA *(and vice versa)*

^ **High-risk for ASCVD:** Typically age ≥ 55 years plus **two or more** risk factors (e.g., hypertension, obesity, smoking, dyslipidemia, albuminuria)
† SGLT2i or SGLT1/2i with proven benefit in patients with heart failure (please note: sotagliflozin is not FDA-approved for glycemic control)

CLASS	ASCVD	HEART FAILURE	RENAL
SGLT2is	**FDA approved CVD benefit:** • canagliflozin • empagliflozin **Neutral:** • bexagliflozin* • dapagliflozin • ertugliflozin	**FDA approved HF benefit:** • dapagliflozin • empagliflozin **Evidence for benefit:** • canagliflozin • ertugliflozin	**FDA approved renal benefit:** • canagliflozin (DKD) • dapagliflozin (CKD) • empagliflozin (CKD) **Neutral:** • bexagliflozin* • ertugliflozin
GLP-1 RAs & GLP-1/GIP RAs *GLP-1/GIP RA tirzepatide is under investigation for CV and renal benefit*	**FDA approved CVD benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ) **Neutral:** • exenatide ER • lixisenatide • semaglutide (oral)	Neutral	**Evidence for renal benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ)

Note: *Sotagliflozin (SGLT1/2 inhibitor) is also a recommended option to provide heart failure benefit in patients with T2DM and heart failure. It is not approved for glycemic control.*

*FDA-approved in 2023; limited data suggests neutral cardiorenal effect.

NOTE: Labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 9/2023.

Select therapies with **adequate efficacy** to achieve and maintain **treatment goals**.

In patients with concurrent **glycemic management** and **weight management goals**, consider therapies with **high** to **very high** glucose-lowering and weight-loss efficacy.

Glucose-Lowering Efficacy

Very High:
Dulaglutide (high-dose)
Semaglutide
Tirzepatide
Insulin
Combination therapy

High:
GLP-1 RA *(not listed above)*
Metformin
SGLT2i
Sulfonylurea
TZD

Intermediate:
DPP-4i

Weight-Loss Efficacy

Very High:
Semaglutide
Tirzepatide

High:
Dulaglutide
Liraglutide

Intermediate:
GLP-1 RA *(not listed above)*
SGLT2i

Intermediate:
DPP-4i
Metformin

Cost and Access

Consider oral options available in generic form or at a lower cost:
- SU or TZD*

**Only pioglitazone is available in a generic formulation*

Consider insulins that are available at lower cost:
- NPH or Regular

Please note: Insulin analogs (or inhaled insulin) are preferred to human insulins due to the lower hypoglycemia risk

Patient assistance programs may be available for certain brand name medications

If A1C above target

Add additional agents based on patient-specific factors including: glycemic goals, cardiorenal risk, comorbidities, cost and access

Do not combine DPP-4i, GLP-1 RA and/or tirzepatide (GLP-1/GIP RA)

More clinical pearls at pyrls.com.

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Type 2 Diabetes Pharmacotherapy

Treatment Algorithm for Glycemic Control (2024 Update)

Comprehensive lifestyle changes and non-insulin agents should generally be considered prior to insulin therapy

Consider **early insulin initiation** with extreme hyperglycemia: BG ≥300 mg/dL, or A1C >10% or signs of catabolism present

See Page 1 regarding non-insulin initial pharmacotherapy use and selection

Reassess treatment plan every **3-6 months** and modify if appropriate

Injectable therapy needed to lower A1C?

Consider **GLP-1 RA** or **GLP-1/GIP RA** in most patients prior to insulin
Titrate to **maintenance dose**

Already on **GLP-1 RA** or **GLP-1/GIP RA**?
GLP-1 RA or GLP-1/GIP RA **not appropriate**?
Or is **insulin preferred**?

Assess basal insulin dose adequacy & evaluate for overbasalization

Evaluate for clinical signs of overbasalization or need for adjunctive therapy:
- Basal dose > ~0.5 units/kg/day
- Elevated bedtime-morning/ post-preprandial differential
- Hypoglycemia (aware/unaware)
- High glycemic variability

Add **basal insulin analog** or **bedtime NPH** based upon patient-specific factors (e.g., cost)

START: 10 units/day or 0.1-0.2 units/kg/day

TITRATE to fasting plasma glucose (FPG) target:
- Follow an evidence-based titration algorithm, e.g., ↑ 2 units every 3 days until FPG target
- Hypoglycemia is never acceptable; titrate at a rate to minimize hypoglycemia risk
- If hypoglycemia occurs for no clear reason, ↓ dose 10-20%

If A1C is above target

On bedtime NPH? Consider conversion to BID NPH

One possible approach:

START:
- Total dose = 80% of current
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:
Based on individual's needs

If A1C is above target

Add prandial insulin

Usually start with one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

START:
- 4 units/day or 10% of basal insulin dose
- If A1C <8%, consider ↓ basal dose by 4 units/day or by 10% of basal dose

TITRATION:
- ↑ dose 1-2 units or 10-15% twice weekly
- If hypoglycemia occurs for no clear reason, ↓ dose by 10-20%

If A1C is above target

Consider BID premix insulin

START:
- Usually unit per unit at the same total insulin dose, but may require adjustment for the individual's needs

TITRATION:
Based on individual's needs

Stepwise additional prandial injections

(i.e. 1 then 2 then 3 injections daily)

Full basal-bolus regimen

(i.e. prandial insulin w/ meals and basal insulin)

Consider self-mixed/split insulin regimen

Can adjust NPH and short/rapid-acting insulins separately

START:
- Total NPH dose = 80% of current NPH
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 units of short/rapid insulin to each injection or 10% of reduced NPH dose

TITRATION:
- Titrate components of the regimen based on the individual's needs

References: American Diabetes Association Professional Practice Committee. American Diabetes Association. Standards of Care in Diabetes - 2024. Diabetes Care 1 January 2024; 47 (Suppl. 1): S1–S321. Individual FDA Prescribing Information labels.

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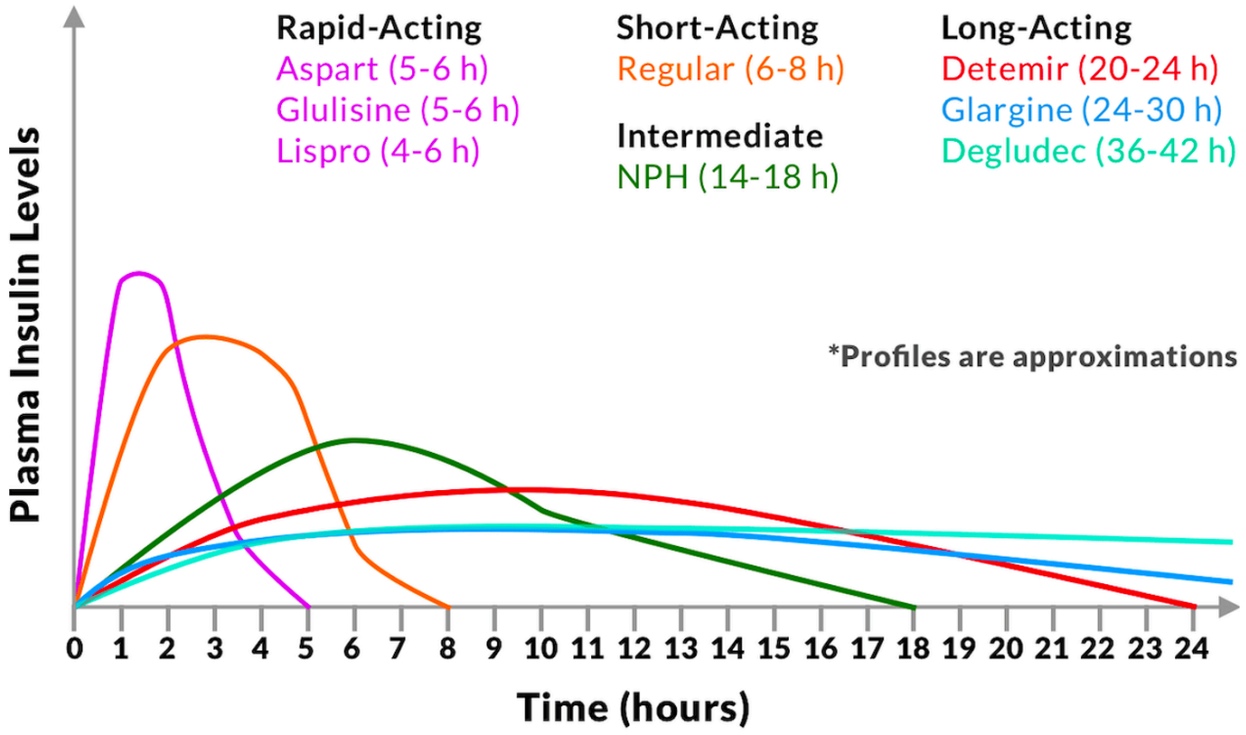
Insulin Classes and Action Profiles



Adapted and referenced from: Hirsch IB. Insulin analogues. N Engl J Med. 2005 Jan 13;352(2):174-83. https://www.ncbi.nlm.nih.gov/pubmed/15647580 and individual product labels.

BRAND	GENERIC	CLASS	DURATION	TYPE
Admelog	Insulin lispro (conventional)	Rapid-acting	4-6 hours	Analog
Afrezza	Inhaled insulin	Rapid-acting	2.5-3 hours	Human
Apidra	Insulin glulisine	Rapid-acting	5-6 hours	Analog
Basaglar	Insulin glargine	Long-acting	24-30 hours	Analog
Fiasp	Insulin aspart (faster-acting)	Rapid-acting	5-6 hours	Analog
HumaLog	Insulin lispro (conventional)	Rapid-acting	4-6 hours	Analog
Humulin N	NPH	Intermediate-acting	14-18 hours	Human
Humulin R (U-100)	Regular insulin	Short-acting	6-8 hours	Human
Humulin R (U-500)	Regular insulin	Intermediate-acting	~21 hours (13-24 hours)	Human
Lantus	Insulin glargine	Long-acting	24-30 hours	Analog
Levemir	Insulin detemir	Long-acting	20-24 hours	Analog
Lyumjev	Insulin lispro-aabc (faster-acting)	Rapid-acting	4-6 hours	Analog
NovoLog	Insulin aspart (conventional)	Rapid-acting	5-6 hours	Analog
Novolin N	NPH	Intermediate-acting	14-18 hours	Human
Novolin R	Regular insulin	Short-acting	6-8 hours	Human
Rezvoglar	Insulin glargine-aglr	Long-acting	24-30 hours	Analog
Semglee	Insulin glargine-yfgn	Long-acting	24-30 hours	Analog
Toujeo	Insulin glargine	Long-acting	24-30 hours	Analog
Tresiba	Insulin degludec	Long-acting	36-42 hours	Analog

Insulin Products

Last Updated 2/2024

Rapid-Acting

100 U/mL vial (3 or 10 mL)
100 U/mL pen (3 mL) - **5 pens**/box

Admelog [SoloStar, Vial]
Insulin lispro (analog, conventional)
Duration: 4-6 hours (or 3-5 hours)

4 U/INH
8 U/INH
12 U/INH
(single-dose cartridges)

Afrezza
Inhaled powdered Insulin (human, ultra-rapid)
Duration: 2.5-3 hours

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box

Apidra [SoloStar, Vial]
Insulin glulisine (analog)
Duration: 5-6 hour (or 3-5 hours)

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box
100 U/mL cart. (3 or 1.6 mL)

Fiasp [FlexTouch, Vial, PenFill, PumpCart]
Insulin aspart (analog, ultra-rapid)
Duration: 4-6 hours (or 3-5 hours)

100 U/mL vial (3 or 10 mL)
100 U/mL pen (3 mL) - **5 pens**/box
200 U/mL pen (3 mL) - **2 pens**/box

HumaLog [KwikPen, Jr, Tempo Pen, Vial]
Insulin lispro (analog, conventional)
Duration: 4-6 hours

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box
200 U/mL pen (3 mL) - **2 pens**/box

Lyumjev [KwikPen, Jr, Tempo Pen, Vial]
Insulin lispro-aabc (analog, ultra-rapid)
Duration: 4-6 hours

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box
100 U/mL cart. (3 mL)

NovoLog [FlexPen, Vial, PenFill]
Insulin aspart (analog, conventional)
Duration: 4-6 hours

Intermediate-Acting

100 U/mL vial (3 or 10 mL)
100 U/mL pen (3 mL) - **5 pens**/box

Humulin N (U-100) [KwikPen, Vial]
Insulin isophane or NPH (human)
Duration: 14-18 hours

500 U/mL vial (20 mL)
500 U/mL pen (3 mL) - **2 pens**/box

Humulin R (U-500) [KwikPen, Vial]
Regular insulin (human)
Duration: ~21 hours (13-24 h)

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box

Novolin N (U-100) [FlexPen, Vial]
Insulin isophane or NPH (human)
Duration: 14-18 hours

Intermediate + Rapid-Acting

50/50 U/mL pen (3 mL) - **5 pens**/box

Humalog Mix 50/50 [KwikPen]
Insulin lispro protamine (50%)/lispro (50%)
Duration: Up to 24 hours (analog)

75/25 U/mL vial (10 mL)
75/25 U/mL pen (3 mL) - **5 pens**/box

Humalog Mix 75/25 [KwikPen, Vial]
Insulin lispro protamine (75%)/lispro (25%)
Duration: 16-20 hours (analog)

70/30 U/mL vial (10 mL)
70/30 U/mL pen (3 mL) - **5 pens**/box

Novolog Mix 70/30 [FlexPen, Vial]
Insulin aspart protamine (70%)/aspart (30%)
Duration: Up to 24 hours (analog)

Long-Acting

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box

Levemir* [FlexPen, Vial]
Insulin detemir (analog)
Duration: 20-24 hours

100 U/mL pen (3 mL) - **5 pens**/box

Basaglar [KwikPen, Tempo Pen]
Insulin glargine (analog)
Duration: 24-30 hours

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box

Lantus [SoloStar, Vial]
Insulin glargine (analog)
Duration: 24-30 hours

100 U/mL pen (3 mL) - **5 pens**/box

Rezvoglar [KwikPen]
Insulin glargine-aglr (analog, biosimilar^)
Duration: Up to 24 hours

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box

Semglee [Pen, Vial]
Insulin glargine-yfgn (analog, biosimilar^)
Duration: 24-30 hours

300 U/mL pen (1.5 mL) - **3 pens**/box
300 U/mL pen (3 mL) - **2 pens**/box

Toujeo [SoloStar, Max]
Insulin glargine (analog)
Duration: Up to 36 hours

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box
200 U/mL pen (3 mL) - **3 pens**/box

Tresiba [FlexTouch, Vial]
Insulin degludec (analog, ultra-long)
Duration: 36-42 hours

Short-Acting

100 U/mL vial (3 or 10 mL)

Humulin R (U-100) [Vial]
Regular insulin (human)
Duration: 6-8 hours

100 U/mL vial (10 mL)
100 U/mL pen (3 mL) - **5 pens**/box

Novolin R [FlexPen, Vial]
Regular insulin (human)
Duration: 6-8 hours

1 U/mL single-dose container (100 mL)

Myxredlin
Regular insulin (human) IV solution

Intermediate + Short-Acting

70/30 U/mL vial (3 or 10 mL)
70/30 U/mL pen (3 mL) - **5 pens**/box

Humulin 70/30 [KwikPen, Vial]
Insulin isophane (70%)/regular insulin (30%)
Duration: Up to 24 hours (analog/human)

70/30 U/mL vial (10 mL)
70/30 U/mL pen (3 mL) - **5 pens**/box

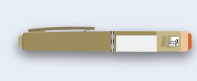
Novolin 70/30 [FlexPen, Vial]
Insulin isophane (70%)/regular insulin (30%)
Duration: Up to 24 hours (analog/human)

Long-Acting + GLP-1 RA

(glucagon-like peptide 1 receptor agonist)

100 U/3.6 mg per mL pen (3 mL) - **5 pens**/box

Xultophy [Pen]
Insulin degludec + liraglutide (analog)
Duration: Up to 42 hours (degludec)



100 U/33 mcg per mL pen (3 mL) - **5 pens**/box

Soliqua [SoloStar]
Insulin glargine + lixisenatide (analog)
Duration: 24-30 hours (glargine)

Insulin Biosimilars

At the time of writing (April 2023), there are **two** insulin biosimilars available in the United States:

1. **Rezvoglar®** (insulin glargine-aglr)
2. **Semglee®** (insulin glargine-yfgn)

Both are **interchangeable** biosimilars of **Lantus®**. It should be noted that these two products are **not biosimilars of Basaglar** (another distinct insulin glargine reference product), nor are they interchangeable with each other. Refer to the **FDA's Purple Book** for the most up-to-date list of approved biosimilars.

⚠ ***Note:** Levemir FlexPen will be **discontinued** from the U.S. market on **April 1, 2024**. Supply disruption of Levemir FlexPen is expected to begin in **mid-January of 2024**. The entire Levemir brand, including the vial, will be **discontinued** on **December 31, 2024**.

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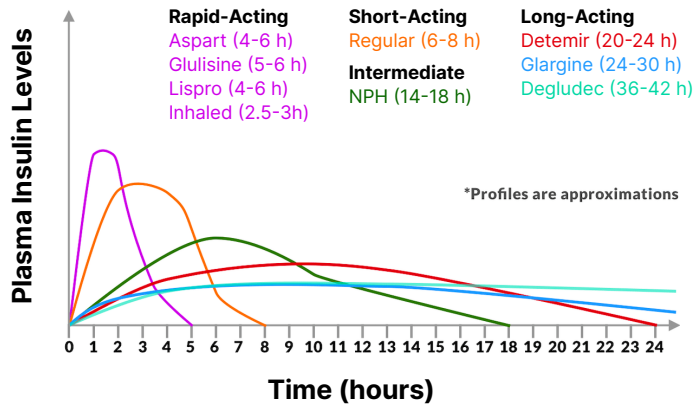
Insulin Products Storage

Last Updated 2/2024

All products are good until their expiration date when kept **unopened and refrigerated** (36°F-46°F [2°C-8°C]).

BRAND	GENERIC	DAYS GOOD AT ROOM TEMP (≤ 86° F [30°C]) WHEN IN-USE	STORAGE WHEN OPENED/IN-USE
Admelog SoloStar pen	Insulin lispro	28 days	**Do not refrigerate**
Admelog vial	Insulin lispro	28 days	Room or Refrigerate (≤ 86° F [30°C])
Apidra SoloStar pen	Insulin glulisine	28 days (≤ 77° F [25°C])	**≤ 77°F (25°C), but do not refrigerate**
Apidra vial	Insulin glulisine	28 days (≤ 77° F [25°C])	Room or Refrigerated (≤ 77°F [25°C])
Basaglar KwikPen/Tempo Pen	Insuline glargine	28 days	**Do not refrigerate**
Fiasp FlexTouch pen	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Fiasp PenFill cartridge	Insulin aspart	28 days	**Do not refrigerate**
Fiasp vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humalog KwikPen and cartridge	Insulin lispro	28 days	**Do not refrigerate**
Humalog vial	Insulin lispro	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humalog Junior KwikPen	Insulin lispro	28 days	**Do not refrigerate**
Humalog TempoPen	Insulin lispro	28 days	**Do not refrigerate**
Humalog Mix 50/50 KwikPen	Insulin lispro protamine/lispro	**10 days**	**Do not refrigerate**
Humalog Mix 75/25 KwikPen	Insulin lispro protamine/lispro	**10 days**	**Do not refrigerate**
Humalog Mix 75/25 vial	Insulin lispro protamine/lispro	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin N KwikPen	NPH	**14 days**	**Do not refrigerate**
Humulin N vial	NPH	**31 days**	Room or Refrigerated (≤ 86°F [30°C])
Humulin R vial	Insulin human (regular)	**31 days**	Room or Refrigerated (≤ 86°F [30°C])
Humulin R U-500 KwikPen	Insulin human (regular)	28 days	**Do not refrigerate**
Humulin R U-500 vial	Insulin human (regular)	**40 days**	Room or Refrigerated (≤ 86°F [30°C])
Humulin 70/30 KwikPen	NPH/regular	**10 days**	**Do not refrigerate**
Humulin 70/30 vial	NPH/regular	**31 days**	Room or Refrigerated (≤ 86°F [30°C])
Lantus SoloStar pen	Insulin glargine	28 days	**Do not refrigerate**
Lantus vial	Insulin glargine	28 days	Room or Refrigerated (≤ 86°F [30°C])
Levemir FlexPen	Insulin detemir	**42 days**	**Do not refrigerate**
Levemir vial	Insulin detemir	**42 days**	Room or Refrigerated (≤ 86°F [30°C])
Lyumjev pen	Insulin lispro-aabc	28 days	**Do not refrigerate**
Lyumjev vial	Insulin lispro-aabc	28 days	Room or Refrigerated (≤ 86°F [30°C])
Novolin N FlexPen	NPH	28 days	**Do not refrigerate**
Novolin N vial	NPH	**42 days (≤ 77° F [25°C])**	**≤ 77°F (25°C), but do not refrigerate**
Novolin R FlexPen	Regular	28 days	**Do not refrigerate**
Novolin R vial	Regular	**42 days (≤ 77° F [25°C])**	**≤ 77°F (25°C), but do not refrigerate**
Novolin 70/30 FlexPen	NPH/Regular	28 days	**Do not refrigerate**
Novolin 70/30 vial	NPH/Regular	**42 days (≤ 77° F [25°C])**	**≤ 77°F (25°C), but do not refrigerate**
NovoLog FlexTouch/FlexPen	Insulin aspart	28 days	**Do not refrigerate**
NovoLog vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
NovoLog PenFill Cartridge	Insulin aspart	28 days	**Do not refrigerate**
NovoLog Mix 70/30 FlexPen	Insulin aspart	**14 days**	**Do not refrigerate**
NovoLog Mix 70/30 Vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Rezvoglar KwikPen	Insulin glargine-aglr	28 days	**Do not refrigerate**
Semglee pen	Insulin glargine-yfgn	28 days	**Do not refrigerate**
Semglee vial	Insulin glargine-yfgn	28 days	Room or Refrigerated (≤ 86°F [30°C])
Soliqua 100/33	Insulin glargine + lixisenatide	28 days (≤ 77° F [25°C])	≤ 77°F (25°C), but do not refrigerate
Toujeo (Max) SoloStar pen	Insulin glargine	**56 days**	**Do not refrigerate**
Tresiba FlexTouch pen	Insulin degludec	**56 days**	Room or Refrigerated (≤ 86°F [30°C])
Tresiba vial	Insulin degludec	**56 days**	Room or Refrigerated (≤ 86°F [30°C])
Xultophy 100/3.6	Insulin degludec + liraglutide	**21 days**	Room or Refrigerated (≤ 86°F [30°C])

Insulin Classes and Action Profiles*



Priming Insulin Pens

Prime insulin pens prior to each injection with **2 units except** the following:

Humulin® R U-500 Kwikpen	5 units
Toujeo® SoloStar	3 units
Toujeo® Max SoloStar	4 units
Xultophy® Pen	Select priming symbol

Reference: [1] Hirsch IB. Insulin analogues. N Engl Med. 2005 Jan 13;352(2): 174-83. https//www.ncbi.nlm.nih.gov/pubmed/15647580. [2] Wong EY, Kroon L. Ultra-Rapid-Acting Insulins: How Fast Is Really Needed?. Clin Diabetes. 2021;39(4):415-423. doi:10.2337/cd20-0119. [3] Individual manufacturer product labels.

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Injection Areas

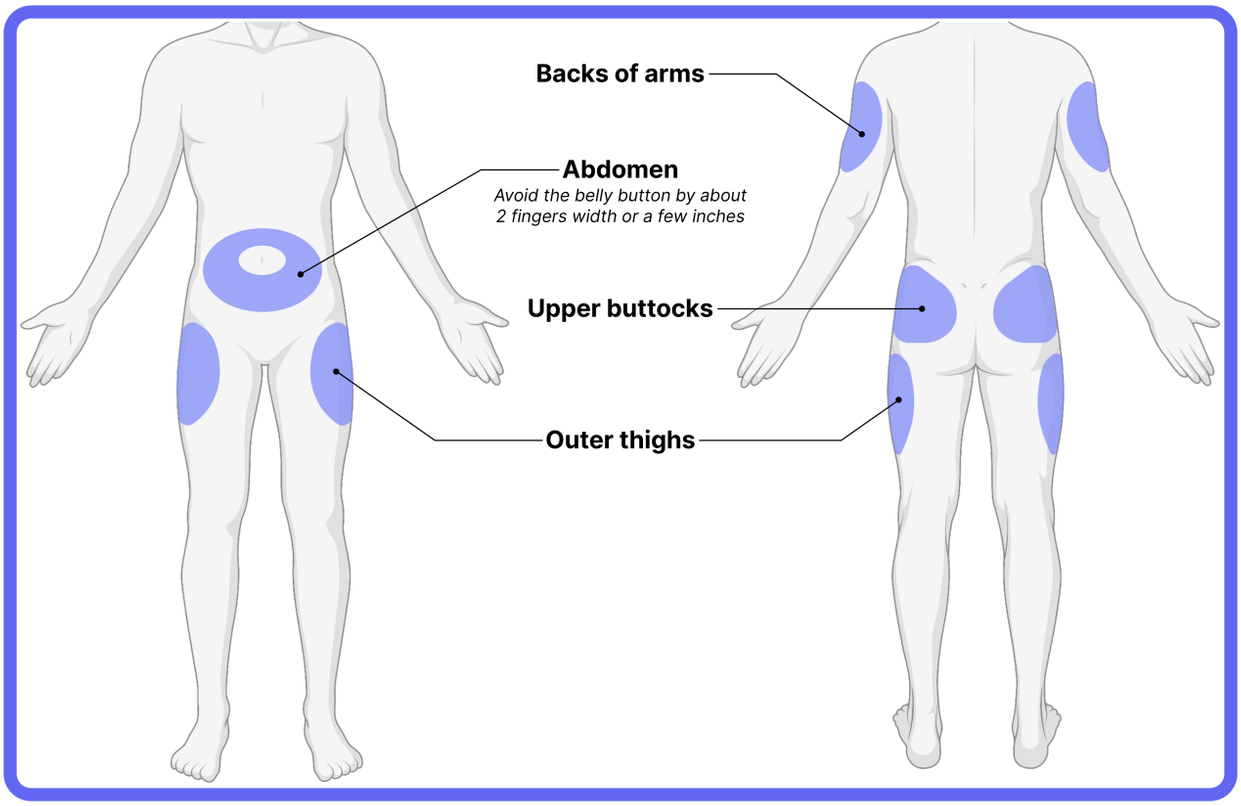
Insulin Injection Areas

Insulin is **best absorbed** when injected into the **abdomen** (staying away from the belly button by about 2 fingers width or a few inches); however, the outer thighs, upper buttocks and backs of arms are also acceptable injection areas.

Using the **same injection area** (e.g., abdomen) for each administration can help ensure the body receives **consistent levels** of insulin.

Rotate injection sites (in the same general body region) to prevent **skin damage**.

If using a **GLP-1 RA** or **GLP-1/GIP RA** with insulin, administer at **separate injection sites** and do **not** mix the medications. The injection sites may be in the same body region but should not be adjacent to each other.



GLP-1 RA and GLP-1/GIP RA Injection Areas

GLP-1 RAs and GLP-1/GIP RAs (e.g., tirzepatide) can be injected into the **abdomen** (staying away from the belly button by about 2 fingers width or a few inches), outer thighs and backs of arms.

Rotate injection sites (in the same general body region) to prevent **skin damage**.

If using a GLP-1 RA or GLP-1/GIP RA with **insulin**, administer at **separate injection sites** and do **not** mix the medications. The injection sites may be in the same body region but should **not** be adjacent to each other.

Cholesterol Management of ASCVD Risk Reduction

Based on the 2018 AHA/ACC/multisociety Guideline on the Management of Blood Cholesterol and the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-C Lowering in the Management of ASCVD Risk

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Secondary ASCVD Prevention in Adults with Clinical ASCVD

Clinical ASCVD includes the following: history of ACS or MI, stable/unstable angina, ischemic stroke/transient ischemic attack, coronary/arterial revascularization or peripheral artery disease (presumed to be of atherosclerotic origin)

Use maximally tolerated statin and consider adding nonstatin therapies to achieve specific **LDL targets** based upon subgroup

Criteria for Defining Very High Risk

***Very high risk ASCVD** is defined as a history of multiple major ASCVD events **or** one major ASCVD event and multiple high-risk conditions

Major ASCVD Events
- Any recent ACS (in last 12 months)
- History of MI (other than recent ACS)
- History of ischemic stroke
- Symptomatic PAD

High-Risk Conditions
- Age ≥65 years
- Heterozygous familial hypercholesterolemia
- History of prior CABG surgery or PCI outside of the major ASCVD event(s)
- Diabetes
- Hypertension
- Chronic kidney disease
- History of congestive heart failure
- Current smoker
- Persistently elevated LDLC (≥100 mg/dL) despite max-tolerated statin and ezetimibe

ASCVD Not at Very High Risk*

Target **≥50%** LDL reduction and LDL **<70 mg/dL**

↓ If not reached on max-tolerated statin ↓

Consider adding **ezetimibe**

↓ If LDL targets not reached ↓

Consider adding **PCSK9 mAb** § (in addition to or in place of ezetimibe)

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Very High Risk ASCVD*

Target **≥50%** LDL reduction and LDL **<55 mg/dL**

↓ If not reached on max-tolerated statin ↓

Consider adding **ezetimibe** and/or **PCSK9 mAb** ¶ §

↓ If LDL targets not reached ↓

Consider adding **second** nonstatin (e.g., ezetimibe + PCSK9 mAb)

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Baseline LDL ≥190 mg/dL without clinical/genetic FH diagnosis

Target **≥50%** LDL reduction and LDL **<70 mg/dL**

↓ If not reached on max-tolerated statin ↓

Consider lipid specialist and RD/RDN referral

Consider adding **ezetimibe** and/or **PCSK9 mAb** ¶ §

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Under care of lipid specialist, if LDL persistently >200 mg/dL consider LDL apheresis

Baseline LDL ≥190 mg/dL with clinical/genetic FH diagnosis

Target **≥50%** LDL reduction and LDL **<55 mg/dL**

↓ If not reached on max-tolerated statin ↓

Consider lipid specialist and RD/RDN referral

Consider adding **ezetimibe** and/or **PCSK9 mAb** ¶ §

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Under care of lipid specialist, if inadequate response to max-tolerated statin with or without ezetimibe/PCSK9 inhibitors:
- Consider LDL apheresis in patients with HeFH or HoFH
- Consider evinacumab or lomitapide in patients with HoFH

¶ **Ezetimibe** may be preferred as the initial nonstatin agent in those requiring **<25%** additional LDL reduction, while a **PCSK9 mAb** may be preferred in those requiring **>25%** additional LDL reduction. The simultaneous addition of two agents may be considered in patients requiring greater LDL reduction than likely achievable with one agent alone.

§ Consider replacing PCSK9 mAb with **inclisiran** in those with PCSK9 mAb adherence or tolerability issues. PCSK9 mAbs (alirocumab, evolocumab) are currently the preferred PCSK9 inhibitors over inclisiran due to available safety and CV outcomes data. If inclisiran is used, it should replace the PCSK9 mAb as there is no evidence or mechanistic plausibility for use together. Consider referral to lipid specialist for use.

Primary ASCVD Prevention

Assess and discuss ASCVD risk in each subgroup, promote healthy lifestyle to reduce ASCVD risk

LDL ≥190 mg/dL

Use max-tolerated statin

Target **≥50%** LDL reduction and LDL **<100 mg/dL**

↓ If LDL targets not reached ↓

Consider lipid specialist & RD/RDN referral

Consider adding **ezetimibe** and/or **PCSK9 mAb** ¶ §

↓ If LDL targets not reached ↓

Consider adding **second** nonstatin (e.g., ezetimibe + PCSK9 mAb)

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Under care of lipid specialist, if **HoFH** and inadequate response to max-tolerated statin with or without ezetimibe/PCSK9 inhibitors:
- Consider LDL apheresis
- Consider evinacumab or lomitapide

Adults with diabetes (LDL <190 mg/dL)

Age 20-39 years

Diabetes-specific risk enhancers*? Consider statin

Age 40-75 years

10-year ASCVD risk ≥7.5%, diabetes-specific risk enhancers*, or subclinical atherosclerosis?

No → **Use moderate-intensity statin**

Target **30-49%** LDL reduction and LDL **<100 mg/dL** (or non-HDL <130 mg/dL)

↓ If LDL targets not reached ↓

Increase to **high-intensity statin**

If LDL targets not reached

Yes → **Use high-intensity statin**

Target **≥50%** LDL reduction and LDL **<100 mg/dL** (or non-HDL <130 mg/dL)

If 10-yr ASCVD Risk ≥20%: Target **≥50%** LDL reduction and LDL **<70 mg/dL** (or non-HDL <100 mg/dL)

↓ If LDL targets not reached ↓

Consider adding **ezetimibe**

May consider bile acid sequestrant if fasting TG <300 mg/dL or if ezetimibe has inadequate response or is not tolerated

Age >75 years

Discuss the risk-benefit of statin prior to initiation

PCSK9 mAbs, inclisiran, and bempedoic acid currently do not have an established place in therapy for primary prevention in patients with diabetes without either ASCVD or baseline LDL ≥190 mg/dL

Adults without diabetes (LDL 70-189 mg/dL)

Age 20-39 years

Generally focus on implementing **healthy lifestyle changes** to reduce lifetime ASCVD risk

Age 40-75 years

Assess 10-year ASCVD risk

<5% Low-Risk

Promote healthy lifestyle to reduce ASCVD risk

5% to <7.5% Borderline-Risk

Consider risk-enhancing factors^ and **discuss** use of **moderate-intensity statin**

Target **30-49%** LDL reduction and LDL **<100 mg/dL**

≥7.5% to <20% Intermediate-Risk

Consider **moderate-intensity statin**

Target **30-49%** LDL reduction and LDL **<100 mg/dL**

≥20% High-Risk

Use high-intensity statin

Target **≥50%** LDL reduction and LDL **<70 mg/dL**

↓ If LDL targets not reached ↓

Consider adding **ezetimibe**

↓ If LDL targets not reached ↓

Increase to **high-intensity statin**

The use of PCSK9 mAbs is not routinely recommended for primary prevention due to limited data

Age > 75 years:

If LDL 70-189 mg/dL, consider initiation of a **moderate-intensity statin** upon **clinician-patient discussion**

If there is **clinical uncertainty** regarding the need for statin therapy in patients with **borderline-** or **intermediate-risk**, their **CAC score** may be used to help reach a decision

CAC = 0 AU	→	Consider **deferring statin** & reassess in 3-5 years (if no high-risk conditions present)	
CAC 1-99 AU and < 75th percentile†	→	Consider **moderate-intensity statin** — Target 30-49% LDL reduction and LDL <100 mg/dL	→ If LDL targets not reached, consider **high-intensity statin**
CAC ≥ 100 AU or ≥ 75th percentile†	→	Consider **moderate- or high-intensity statin** — Target LDL % reduction based on statin intensity and achieve LDL <70 mg/dL	→ If LDL targets not reached **consider ezetimibe**
CAC ≥ 1000 AU	→	Consider **high-intensity statin** — Target ≥50% LDL reduction and LDL <70 mg/dL	→ If LDL targets not reached consider **ezetimibe**, then consider **PCSK9 mAb**

† percentile for corresponding age/sex/race

¶ **Ezetimibe** may be preferred as the initial nonstatin agent in those requiring **<25%** additional LDL reduction, while a **PCSK9 mAb** may be preferred in those requiring **>25%** additional LDL reduction. The simultaneous addition of two agents may be considered in patients requiring greater LDL reduction than likely achievable with one agent alone.

§ Consider replacing PCSK9 mAb with **inclisiran** in those with PCSK9 mAb adherence or tolerability issues. PCSK9 mAbs (alirocumab, evolocumab) are currently the preferred PCSK9 inhibitors over inclisiran due to available safety and CV outcomes data. If inclisiran is used, it should replace the PCSK9 mAb as there is no evidence or mechanistic plausibility for use together. Consider referral to lipid specialist for use.

*Diabetes-Specific Risk Enhancers

- Long duration of diabetes (≥10 years for type 2, ≥20 years for type 1)
- UACR ≥30
- eGFR <60 mL/min
- Retinopathy
- Neuropathy
- ABI <0.9

*ASCVD Risk Score ↗

^Risk-Enhancing Factors

Medical History/Demographics
- Family history of premature ASCVD (males <55 years; females <65 years)
- Primary hypercholesterolemia (LDL 160-189 mg/dL)
- Chronic kidney disease (with or without albuminuria)
- Metabolic syndrome
- History of premature menopause (before age 40) or preeclampsia
- Chronic inflammatory disorders (e.g., psoriasis, RA, HIV/AIDS)
- High-risk race/ethnicities (e.g., South Asian ancestry)

Biomarkers
- Persistently elevated, primary hypertriglyceridemia (≥ 175 mg/dL)
- CRP ≥2.0 mg/dL
- Lp(a) level ≥50 mg/dL (or >125 nmol/L)
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

ACS: acute coronary syndrome
apoB: apolipoprotein B
ASCVD: atherosclerotic cardiovascular disease
AU: Agatston unit
BAS: bile acid sequestrant
CAC: coronary artery calcium
CRP: C-reactive protein
FH: familial hypercholesterolemia
HDL: high-density lipoprotein cholesterol
HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
LDL: low-density lipoprotein cholesterol
Lp(a): lipoprotein (a)
MI: myocardial infarction
PAD: peripheral artery disease
PCSK9 mAb: proprotein convertase subtilisin/kexin type 9 monoclonal antibody
RD/RDN: registered dietitian/dietitian nutritionist
UACR: urine albumin creatinine ratio

References: Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. [2] Writing Committee, Lloyd-Jones DM, Morris PB, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Statins Comparison

Statin Medication	Low Intensity <30% LDL ↓	Moderate Intensity 30–49% LDL ↓	High Intensity ≥50% LDL ↓	Dose Timing	Take with Food?	Grapefruit	Myopathy Risk
Atorvastatin Lipitor®		10-20 mg	40-80 mg	Any	With or without	Avoid	Low
Fluvastatin Lescol®	20-40 mg	40 mg BID		PM (unless BID)	With or without	No effect	Very low
Fluvastatin ER Lescol XL®		80 mg XL		Any	With or without	No effect	Very low
Lovastatin Mevacor®	20 mg	40-80 mg		PM (unless BID)	With food	Avoid	Moderate
Lovastatin ER Altoprev®	20 mg	40-80 mg		Bedtime	Not specified†	Avoid	Moderate
Pitavastatin Livalo®, Zypitamag®		1-4 mg*		Any	With or without	No effect	Very low
Pravastatin Pravachol®	10-20 mg	40-80 mg		Any	With or without	No effect	Very low
Rosuvastatin Crestor®, Ezallor®		5-10 mg	20-40 mg	Any	With or without	No effect	Low
Simvastatin Zocor®, FloLipid®	10 mg	20-40 mg^		PM	With or without	Avoid	Moderate

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*Some sources reference pitavastatin 1 mg as low intensity.
^Simvastatin 80 mg may be considered moderate or high intensity; however, this dose is not recommended due to ↑ risk of myopathy/rhabdomyolysis.
† The manufacturer's prescribing information does not specify whether or not each dose has to be taken with food.
Statin dose intensities reference: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

Pharmacotherapy for COPD

Based on the 2024 Global Initiative for Chronic Lung Disease (GOLD) Report

Reference: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2024 Report). https://goldcopd.org/2024-gold-report/.

COPD Treatment Goals

Stable COPD

- **Improve:** symptoms, exercise tolerance, health
- **Reduce risks of:** disease progression, exacerbations, death

COPD Exacerbations

- **Minimize** the effects of the exacerbation
- **Prevent** future exacerbations

Initiation of Pharmacotherapy in Stable COPD

Select initial pharmacotherapy based upon current symptoms and exacerbations history

Exacerbations

≥ 2 moderate exacerbations OR ≥1 resulting in hospital admission

E

LABA + LAMA

- If eos ≥ 300, consider LABA + LAMA + **ICS**
- Consider single-inhaler options for patient convenience

≤ 1 moderate exacerbations not resulting in hospital admission

A

Bronchodilator
Either long- or short-acting

LABA, LAMA, SABA or SAMA

- Long-acting generally preferred unless very occasional dyspnea
- SABA + SAMA combination more effective than either alone

CAT < 10, mMRC 0-1

B

LABA + LAMA

- Consider single-inhaler options for convenience

CAT ≥ 10, mMRC ≥ 2

Symptoms

CAT: COPD Assessment Test
mMRC: Modified Medical Research Council dyspnea scale

Pharmacotherapy Key Points

Inhaled Medications

- Choice of inhaler device should be individualized for optimal efficacy, access, cost, patient preference, and ability to properly use
- Must ensure proficiency in proper use of inhalers; educate and demonstrate
- Assess inhaler technique and adherence prior to therapy modification

Bronchodilators

- Bronchodilators are first-line for all diagnosed with COPD
- Long-acting agents (e.g., LABA, LAMA) are preferred over short-acting (e.g., SABA, SAMA), except in those with only occasional dyspnea and when immediate relief is needed in those on long-acting maintenance therapy
- Combination of [LAMA + LABA] is preferred when starting treatment with long-acting bronchodilators; patients not controlled on a single long-acting bronchodilator should be escalated to dual (more effective)
- LAMAs provide greater exacerbation risk reduction than LABAs
- Combination of [SABA + SAMA] is more effective than either alone
- Inhaled bronchodilators are recommended over oral bronchodilators
- Theophylline is not recommended unless other bronchodilators are either unavailable or unaffordable for long-term treatment

Anti-Inflammatory Agents

- Long-term monotherapy with ICS/oral steroids is not recommended; low efficacy, increases risk for side effects (e.g., pneumonia)
- If ICS indicated, [ICS + LABA + LAMA] is superior to & preferred over [LABA + ICS]; [ICS + LABA + LAMA] has proven mortality benefit versus [LABA + LAMA] in those with symptomatic COPD and history of exacerbations
- ICS can be added to [LABA + LAMA] regimens to improve symptoms and reduce exacerbations in those with signs of inflammation (e.g., comorbid asthma, eos ≥ 300 or present with an exacerbation history)
  - ICS **should** be included if features of asthma are present
- Addition of PDE4 inhibitor to [LABA + LAMA (+/- ICS)] may be considered in those with severe to very severe airflow limitation, chronic bronchitis, and exacerbations
- In those with exacerbations despite appropriate therapy, macrolides (e.g., azithromycin) may be considered (especially in former smokers)

Follow-Up Pharmacotherapy Management in Stable COPD

COPD management is an individualized, continuous cycle of assessment and treatment adjustment

Is COPD controlled?

Review:
- Symptoms (e.g., dyspnea)
- Exacerbations

Assess:
- Inhaler technique and adherence
- Non-pharmacological interventions

Adjust:
- Consider escalation or de-escalation
- Switch device or molecules

No

Continue current therapy

Primary Issue?*

Dyspnea (shortness of breath)

LAMA or LABA

↓

LAMA + LABA**

↓

- Consider switching inhaler/medication
- Optimize non-pharmacological interventions
- Assess and address other causes of symptoms

Exacerbations

LAMA or LABA

↓

eos < 300? → **No** → **LAMA + LABA****

↓

eos ≥ 100? → **No** → **LAMA + LABA + ICS****
(Consider **de-escalating** to LAMA + LABA if significant side effects occur with ICS)

- **Roflumilast** if FEV1 < 50% + chronic bronchitis
- **Azithromycin**, especially in former smokers

Although [LABA + ICS] is not preferred in treatment of COPD without features of asthma, if the patient has already been on [LABA + ICS] for any reason and is well controlled, the current therapy may be continued.
- If further exacerbations occur, escalate to [LABA + LAMA + ICS] (if eos ≥ 100) **or** switch to [LABA + LAMA] (if eos < 100)
- If major symptoms are present, consider switching to [LABA + LAMA]

*If both dyspnea and exacerbation must be addressed, **use the exacerbation pathway**
**For patients on [LAMA + LABA] or [LAMA + LABA + ICS], single-inhaler options should be considered for convenience

Inhalers Chart & Administration Guides

eos: Blood eosinophil count
ICS: Inhaled corticosteroid
LABA: Long-acting beta-agonist
LAMA: Long-acting muscarinic antagonist
SABA: Short-acting beta-agonist
SAMA: Short-acting muscarinic antagonist

Pharmacotherapy Management of Acute Exacerbations*

*Non life-threatening

Initial Treatment: SABA
(with or without SAMA)

- Initiate maintenance with **long-acting bronchodilators** as soon as stable
  - Consider adding **ICS** to [LAMA + LABA] if frequent exacerbations with ↑ eos
- If severe exacerbation, consider **systemic corticosteroids** (duration: generally **≤5 days**)
- If indicated (e.g., signs of bacterial infection), give **antibiotics** (duration: **5-7 days**)

Heart Failure Pharmacotherapy

Based on the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure and the 2023 ACC Expert Consensus Decision Pathway on Management of HFpEF

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More clinical pearls at pyrls.com

References:
[1] Classes of Heart Failure. American Heart Association. May 31, 2017. https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure
[2] Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2022 May 3;145(18):e1033]. Circulation. 2022;145(18):e895-e1032. doi:10.1161/CIR.0000000000001063
[3] Kittleson M, Panjrath G, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2023. doi:10.1016/j.jacc.2023.03.393

Heart Failure Categories

Stage

A
At risk for HF
- No HF signs/symptoms
- No structural/functional heart disease
- No abnormal biomarkers

B
Pre-HF
- No HF signs/symptoms
- **ONE** of the following:
  (1) Structural heart disease
  (2) ↑ filling pressures
  (3) Risk factors **PLUS** ↑ natriuretic peptides **OR** persistently ↑ cardiac troponin w/o competing diagnosis

C
Symptomatic HF
- Structural heart disease **AND**
- Current or previous HF symptoms

D
Advanced HF
- HF symptoms interfering with normal activity and/or recurrent HF hospitalizations (despite GDMT)

LVEF

HFrEF *(reduced EF)* — **LVEF ≤ 40%**

HFimpEF *(improved EF)* — **LVEF > 40%** *(upon follow up after a previous measurement of LVEF ≤ 40%)*

HFmrEF *(mildly reduced EF)* — **LVEF 41-49%** *(w/ evidence of spontaneous/provokable ↑ LV filling pressures)*

HFpEF *(preserved EF)* — **LVEF ≥ 50%** *(w/ evidence of spontaneous/provokable ↑ LV filling pressures)*

NYHA Class

I
- No symptoms from ordinary daily activities

II
- No symptom at rest
- Ordinary daily physical activities cause HF symptoms

III
- No symptom at rest
- Activities lighter than ordinary daily physical activities cause HF symptoms

IV
- Symptoms at rest
- Discomfort worsens with physical activities

Goals of Therapy

Stage A
- Primary prevention of heart failure

Stage B
- Prevention of clinical heart failure

Stage C
- Reduction of mortality
- Reduction of heart failure symptoms and hospitalization risk
- Elimination of potential barriers to self-care

Stage D
- Provision of inotropic support until mechanical circulatory support or cardiac transplantation is available
- Palliative symptom control and functional improvement (if not eligible for mechanical circulatory support or cardiac transplantation)

Pharmacotherapy Recommendations

Stage A
- Control BP in patients with hypertension
- SGLT2i in patients with T2DM **plus:**
  - Established CVD **or,**
  - High CV risk
- Manage existing comorbidities

Stage B
- ACEi and evidence-based BB in patients with LVEF ≤ 40%
  - If LVEF ≤ 40% **and recent MI**, use ARB if ACEi is not tolerated

Stage C (HFpEF)
- SGLT2i in **all patients** with HFpEF *(unless contraindicated)*
- May consider MRA and/or ARNi if LVEF < 55-60%
  - May consider regardless of LVEF for female patients
  - May consider ARB if unable to receive ARNi therapy
- PRN loop diuretic

Stage C (HFmrEF)
- PRN diuretics (**loop** preferred)
- SGLT2i may be beneficial
- May consider MRA, ACEi/ARB/ARNi, and evidence-based BB *particularly* if LVEF is closer to **HFrEF threshold**

Stage C (HFimpEF)
- Continue GDMT
  - Even if asymptomatic

Stage C (HFrEF)

All patients
- **ARNi** or **ACEi** or **ARB**
  - ARNi: NYHA class II-III
  - ACEi or ARB: NYHA class II-IV
  - Order of preference: ARNi > ACEi > ARB
  - **36-hour washout** required when switching between ACEi and ARNi (and vice versa)
- **Beta Blocker** (evidence-based)
  - Bisoprolol, carvedilol, metoprolol succinate
- **MRA** (e.g. eplerenone, spironolactone)
  - NYHA class II-IV
  - eGFR > 30 mL/min/1.73m2
  - Serum potassium < 5 mEq/L
- **SGLT2i**
  - With or without T2DM
- **Diuretics** (as needed)
  - Loop diuretics preferred

Specific patients
- **Hydralazine + isosorbide dinitrate**
  - African American patients on optimal therapy
  - NYHA class III-IV
- **Ivabradine**
  - NYHA class II-III and LVEF **≤ 35%**
  - On GDMT including **max tolerated BB**
  - NSR with resting HR ≥ 70 BPM
- **Vericiguat**
  - NYHA class II-IV and LVEF **< 45%**
  - Recent HF worsening
  - ↑ BNP or NT-proBNP
- **Digoxin**
  - If symptomatic despite GDMT **or**
  - Unable to tolerate GDMT
- **Potassium binders**
  - e.g., **Patiromer**, **sodium zirconium cyclosilicate**
  - Patients with hyperkalemia (K+ ≥ 5.5 mEq/L) while on RAASi
- **Omega-3 PUFA** (may consider as an adjunct)
  - NYHA class II-IV

Selected Medications That May Cause or Exacerbate HF

COX inhibitors (e.g., NSAIDs)	• ↑ H2O retention, ↑ vascular resistance, ↓ response to diuretics • **Immediate** onset, **major** induction/precipitation of HF
Thiazolidinediones	• Potential blockage of calcium channel • **Intermediate** onset, **major** induction/precipitation of HF
Saxagliptin, Alogliptin	• Mechanism is unclear • **Immediate or delayed** onset, **major** induction/precipitation of HF
Flecainide, Disopyramide	• Proarrhythmic, negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Sotalol	• Proarrhythmic effects, beta blockade • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Dronedarone	• Negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Doxazosin	• Beta-1 stimulation, ↑ renin and aldosterone • **Intermediate to delayed** onset, **moderate** induction/precipitation of HF
Diltiazem, Verapamil	• Negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Nifedipine	• Negative inotropic effects • **Immediate to intermediate** onset, **moderate** induction/precipitation of HF

Recreated from Table 13 from the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Abbreviations

ACEi: angiotensin-converting enzyme inhibitors
ARB: angiotensin (II) receptor blocker
ARNi: angiotensin receptor-neprilysin inhibitors
BB: beta-blocker
BNP: B-type natriuretic peptide
BP: blood pressure
CVD: cardiovascular disease
eGFR: estimated glomerular filtration rate
GDMT: guideline-directed medical therapy
HF: heart failure
HFimpEF: heart failure with improved ejection fraction
HFmrEF: heart failure with mildly reduced ejection fraction
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
LV: left ventricular
LVEF: left ventricular ejection fraction
MI: myocardial infarction
MRA: mineralocorticoid receptor antagonist
NT-proBNP: N-terminal prohormone of B-type natriuretic peptide
NYHA: New York Heart Association
PRN: as needed
PUFA: polyunsaturated fatty acid
RAASi: renin-angiotensin-aldosterone system inhibitor
SGLT2i: sodium-glucose cotransporter-2 inhibitor
T2DM: type 2 diabetes mellitus

Hypertension Management

Based on the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Blood Pressure Categories

BP Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal Blood Pressure	<120	AND	<80
Elevated Blood Pressure	120-129	AND	<80
Stage 1 Hypertension	**130-139**	**OR**	**80-89**
Stage 2 Hypertension	**≥140**	**OR**	**≥90**

Use average of **≥2 BP readings** obtained on **≥2 occasions**

Hypertension Treatment Goals

Goal for all **ages <65 years** with hypertension, regardless of chronic comorbidities, if tolerated is **<130/80 mmHg**

BP goal for **ages ≥65 years** is **<130 mmHg** (SBP)

Reasonable to adjust BP goal based on patient factors including: high comorbidity burden, life expectancy, clinical judgment, patient preference,

Hypertension Treatment Algorithm

Normal BP
<120/<80 mmHg

- Promote healthy lifestyle habits
- Reassess Annually

Elevated BP
120-129/<80 mmHg

- Nonpharmacological interventions
- Reassess in 3-6 months

Stage 1 Hypertension
SBP 130-139 or DBP 80-89 mmHg

Clinical CVD, estimated 10-year ASCVD risk of ≥10%?

Yes

- Nonpharmacological interventions
- \+
- Drug treatment for BP reduction
  - Ideally use first-line agents, otherwise those preferred for existing comorbidities, or based on tolerability
- Reassess BP & adherence in **1 month**; assess tolerability sooner as needed

If BP is above goal

- Titrate dose as tolerated
- If dosing is optimized then add additional drug; first use either first-line agents, those preferred for existing comorbidities, or based on tolerability
- Do not combine ACEi, ARB, or aliskiren

No

- Nonpharmacological interventions
- Reassess in 3-6 months

Stage 2 Hypertension
SBP ≥140 or DBP ≥90 mmHg

- Nonpharmacological interventions
- \+
- Drug treatment for BP reduction
  - Consider 2 agents from different drug classes, especially if BP >20/10 mmHg above goal
  - Use first-line agents, those preferred for existing comorbidities, or based on tolerability
  - Do not combine ACEi, ARB, or aliskiren
- Reassess BP & adherence in **1 month**; assess tolerability sooner as needed

If BP is above goal

- Titrate dose as tolerated
- If dosing is optimized then add additional drug; first use either first-line agents, those preferred for existing comorbidities, or based on tolerability
- Do not combine ACEi, ARB, or aliskiren

Antihypertensive Medications

Primary Medications (Generally First-Line)

Thiazide diuretics e.g. chlorthalidone, indapamide hydrochlorothiazide, metolazone	• Chlorthalidone preferred: long half-life, evidence for CVD benefit • HCTZ: may be cheaper, more widely available, more tolerable • Monitor electrolytes: hyponatremia, hypokalemia, uric acid, calcium
ACE inhibitors e.g. lisinopril, benazepril, enalapril, ramipril, etc.	• Do not combine with ARBs or aliskiren • Risk of hyperkalemia, esp. with CKD, K supplements, K-sparing drugs • Avoid in pregnancy
ARBs e.g. losartan, valsartan, olmesartan, etc.	• Do not combine with ACEis or aliskiren • Risk of hyperkalemia, esp. with CKD, K supplements, K-sparing drugs • Avoid in pregnancy
CCBs, dihydropyridines e.g. amlodipine, felodipine, etc.	• Dose-related lower leg edema, more common in females • Avoid use with HFrEF; use amlodipine or felodipine if required
CCBs, non-dihydropyridines* e.g. diltiazem, verapamil	• *Generally less preferred than the dihydropyridine CCBs • Avoid regular use with BBs due to risk of bradycardia and heart block • Do not use with HFrEF • Drug interactions: both are CYP3A4 substrates, moderate inhibitors

Secondary Medications

Beta-blockers e.g. atenolol, metoprolol, carvedilol, bisoprolol, labetalol, nebivolol, etc.	• May be first-line with compelling indication (e.g. IHD, post-MI, HF) • HFrEF preferred agents: metoprolol *succinate*, carvedilol, bisoprolol • Bronchospastic airway disease preferred: atenolol, metoprolol, bisoprolol • Generally avoid use of BBs with intrinsic sympathomimetic activity (e.g. acebutolol, pindolol, penbutolol), especially with IHD or HF • Avoid abrupt cessation: risk of rebound tachycardia
Loop diuretics furosemide, torsemide, bumetanide	• Preferred diuretics with symptomatic HF • Preferred over thiazides with significant CKD (GFR <30 mL/min)
K-sparing diuretics triamterene, amiloride	• Minimal antihypertensive effect; used to protect from hypokalemia • Avoid in patients with significant CKD (GFR <45 mL/min)
Aldosterone antagonists spironolactone, eplerenone	• Preferred add-on with resistant HTN and in primary aldosteronism • K-sparing diuretic effect: avoid with K-sparing diuretics, or CKD • Spironolactone > risk of gynecomastia, impotence than eplerenone
Alpha-1 blockers doxazosin, prazosin, terazosin	• May be considered second-line in those with concomitant BPH • Risk for orthostatic hypotension, especially in older adults
Direct vasodilators hydralazine, minoxidil	• Use w/ a diuretic and BB: causes fluid retention and reflex tachycardia • Hydralazine has risk of drug-induced lupus-like syndrome • Minoxidil has risk of hirsutism and requires use with a loop diuretic
Central alpha-2 agonists clonidine, guanfacine, methyldopa	• Generally last-line due to CNS adverse effects, orthostatic hypotension • Avoid abrupt cessation: risk of rebound hypertension (esp. clonidine)

Reference: Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in J Am Coll Cardiol. 2018 May 15;71(19):2275-2279]. J Am Coll Cardiol. 2018;71(19):e127-e248. doi:10.1016/j.jacc.2017.11.006

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Smoking Cessation Pharmacotherapy Options

DRUG	USUAL DOSE		RX OR OTC?
NON-NICOTINE THERAPIES			
Varenicline (Chantix) 0.5 mg and 1 mg tablets	**Starting titration:** **Maintenance dose:**	0.5 mg x 3 days, 0.5 mg twice daily x 4 days, 1 mg twice daily starting Day 8 on quit date 1 mg twice daily	Rx
Bupropion SR (Zyban) 150 mg SR tablets	**Starting titration:** **Maintenance dose:**	150 mg once daily AM x 3 days, then 150 mg twice daily x 4 days, quit on day 8 150 mg twice daily	Rx
NICOTINE REPLACEMENT THERAPIES (NRT)			
Nicotine Transdermal Patch 21 mg, 14 mg, 7 mg options	**Smoking >10 cigarettes/day:** **Smoking ≤ 10 cigarettes/day:**	Use 21 mg patch per day for weeks 1-6, then use 14 mg patch per day for weeks 7-8, then use 7 mg patch per day for weeks 9-10 Use 14 mg patch per day for weeks 1-6, then use 7 mg patch per day for weeks 7-8	Rx OTC
Nicotine Gum	**First cigarette *within 30 min* of waking up:** **First cigarette *after 30 min* of waking up:**	4 mg gum PRN every 1-2 hours for cravings, decrease interval of use over 12 weeks 2 mg gum PRN every 1-2 hours for cravings, decrease interval of use over 12 weeks	Rx OTC
Nicotine lozenge or Nicotine mini-lozenge	**First cigarette *within 30 min* of waking up:** **First cigarette *after 30 min* of waking up:**	4 mg lozenge PRN every 1-2 hours for cravings, decrease interval of use over 12 weeks 2 mg lozenge PRN every 1-2 hours for cravings, decrease interval of use over 12 weeks	Rx OTC
Nicotine Inhaler	**Continuously puff for 20 minutes PRN** for smoking cravings. (Use 6-16 cartridges per day for up to 12 weeks) Decrease interval of use over time.		Rx
Nicotine Nasal Spray	Use 1-2 doses/hour (dose = 1 spray per nostril), **not exceeding 5 doses/hour.** **Max duration of therapy:** 3 months		Rx

DRUG	PRECAUTIONS	CONTRAINDICATIONS
NON-NICOTINE THERAPIES		
Varenicline *(Chantix)*	• Severe renal impairment (dose adjustment necessary for CrCl <30 ml/min) • Pregnancy (Category C) and breastfeeding • Adolescents (<18 years of age) • Treatment-emergent neuropsychiatric symptoms	• History of serious hypersensitivity reactions to varenicline or its components
Bupropion SR *(Zyban)*	• Concomitant therapy with medications or conditions known to lower seizure threshold • Hepatic impairment • Pregnancy (Category C) and breastfeeding • Adolescents (<18 years of age) • Treatment-emergent neuropsychiatric symptoms	• Seizure disorder • Concomitant bupropion treatment • Current or prior dx of bulimia or anorexia nervosa • Simultaneous abrupt discontinuation of alcohol or sedatives/benzodiazepines • MAO inhibitors during preceding 14 days; concurrent use of reversible MAO inhibitors
NICOTINE REPLACEMENT THERAPIES (NRT)		
Nicotine Transdermal Patch **Nicotine Gum** **Nicotine Lozenge**	• Recent (<2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy and/or breastfeeding • Adolescents (<18 years of age) • Temporomandibular joint disease *(gum only)*	
Nicotine Nasal Spray	*All above OTC nicotine precautions **PLUS**:* • underlying chronic nasal disorders • severe reactive airway disease	
Nicotine Inhaler	*All above OTC nicotine precautions **PLUS**:* • underlying bronchospastic disease	

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Complete Regimens

Atripla®
Efavirenz (EFV) +
Tenofovir disoproxil fumarate (TDF) +
Emtricitabine (FTC)

Biktarvy®
Bictegravir (BIC) +
Tenofovir alafenamide (TAF) +
Emtricitabine (FTC)

Cabenuva®
Cabotegravir (CAB) +
Rilpivirine (RPV)

Complera®
Rilpivirine (RPV) +
Tenofovir disoproxil fumarate (TDF) +
Emtricitabine (FTC)

Delstrigo®
Doravirine (DOR) +
Tenofovir disoproxil fumarate (TDF) +
Lamivudine (3TC)

Dovato®
Dolutegravir (DTG) +
Lamivudine (3TC)

Genvoya®
Elvitegravir (EVG) + Cobicistat (COBI) +
Tenofovir alafenamide (TAF) +
Emtricitabine (FTC)

Juluca®
Dolutegravir (DTG) +
Rilpivirine (RPV)

Odefsey®
Rilpivirine (RPV) +
Tenofovir alafenamide (TAF) +
Emtricitabine (FTC)

Stribild®
Elvitegravir (EVG) + Cobicistat (COBI) +
Tenofovir disoproxil fumarate (TDF) +
Emtricitabine (FTC)

Symfi®
Efavirenz (EFV) +
Tenofovir disoproxil fumarate (TDF) +
Lamivudine (3TC)

Symfi Lo®
Efavirenz (EFV) (lower dose) +
Tenofovir disoproxil fumarate (TDF) +
Lamivudine (3TC)

Symtuza®
Darunavir (DRV) + Cobicistat (COBI) +
Tenofovir alafenamide (TAF) +
Emtricitabine (FTC)

Triumeq®
Dolutegravir (DTG) +
Abacavir (ABC) +
Lamivudine (3TC)

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Cimduo®
Tenofovir disoproxil fumarate (TDF) +
Lamivudine (3TC)

Combivir®
Zidovudine (ZDV) +
Lamivudine (3TC)

Descovy®
Tenofovir alafenamide (TAF) +
Emtricitabine (FTC)

Emtriva®
Emtricitabine (FTC)

Epivir®
Lamivudine (3TC)

Epzicom®
Abacavir (ABC) +
Lamivudine (3TC)

Retrovir®
Zidovudine (ZDV)

Temixys®
Tenofovir disoproxil fumarate (TDF) +
Lamivudine (3TC)

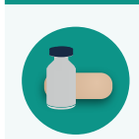
Trizivir®
Abacavir (ABC) +
Lamivudine (3TC) +
Zidovudine (ZDV)

Truvada®
Tenofovir disoproxil fumarate (TDF) +
Emtricitabine (FTC)

Viread®
Tenofovir disoproxil fumarate (TDF)

Ziagen®
Abacavir (ABC)

Capsid Inhibitors



Sunlenca®
Lenacapavir (LEN)

Protease Inhibitors (PIs)

Aptivus®
Tipranavir (TPV)

Evotaz®
Atazanavir (ATV) +
Cobicistat (COBI)

Invirase®
Saquinavir (SQV)

Kaletra®
Lopinavir (LPV) +
Ritonavir (RTV)

Lexiva®
Fosamprenavir (FPV)

Prezcobix®
Darunavir (DRV) +
Cobicistat (COBI)

Prezista®
Darunavir (DRV)

Reyataz®
Atazanavir (ATV)

Entry Inhibitors

Fuzeon®
Enfuvirtide (T-20)
(Fusion Inhibitor)

Rukobia®
Fostemsavir (FTR)
(Attachment Inhibitor)

Selzentry®
Maraviroc (MVC)
(CCR5 Antagonist)

Trogarzo®
Ibalizumab-uiyk (IBA)
(Post-attachment Inhibitor)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Edurant®
Rilpivirine (RPV)

Intelence®
Etravirine (ETR)

Pifeltro®
Doravirine (DOR)

Sustiva®
Efavirenz (EFV)

Viramune®
Nevirapine (NVP)

Integrase Inhibitors (INSTIs)

Isentress®
Raltegravir (RAL)

Tivicay®
Dolutegravir (DTG)

Vocabria® (Oral)
Apretude® (IM)
Cabotegravir (CAB)
Note: IM cabotegravir (Apretude®) is only FDA-approved for HIV PrEP

PK Boosters

Norvir®
Ritonavir (RTV)

Tybost®
Cobicistat (COBI)

Drug Name Abbreviations

Abbreviation	Full Drug Name
3TC	Lamivudine
ABC	Abacavir
ATV	Atazanavir
BIC	Bictegravir
CAB	Cabotegravir
COBI or c	Cobicistat
DOR	Doravirine
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
ETR	Etravirine
EVG	Elvitegravir
FPV	Fosamprenavir
FTC	Emtricitabine
FTR	Fostemsavir
IBA	Ibalizumab
LEN	Lenacapavir
LPV	Lopinavir
MVC	Maraviroc
NVP	Nevirapine
RAL	Raltegravir
RPV	Rilpivirine
RTV or r	Ritonavir
SQV	Saquinavir
T-20	Enfuvirtide
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TPV	Tipranavir
ZDV	Zidovudine

Not Recommended

These antiretroviral agents are no longer recommended for HIV treatment due to various reasons including poor efficacy, toxicity, pill burden, and pharmacology:

- Delavirdine (DLV)
- Didanosine (ddI)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Stavudine (d4T)

Source: *Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed 03/10/2023.*

HIV Medications

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Management of Community-Acquired Pneumonia (CAP) in Non-Pregnant Adults

Clinical syndrome consistent with CAP based on signs/symptoms AND infiltrate on chest radiography

Determine outpatient VS inpatient treatment based on:

- ☐ Clinical judgment **AND**
- ☐ Clinical prediction rule for prognosis
  - ☐ Pneumonia Severity Index (PSI) preferred over CURB-65

Reference: AM J Respir Crit Care Med; 2019; 200(7):

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OUTPATIENT *

Assess for comorbidities

- Chronic heart, lung, liver or renal
- Diabetes
- Alcoholism
- Malignancy
- Asplenia

NO → **Recommended empiric therapy**

Amoxicillin 1 gram three times daily
OR
Doxycycline 100 mg twice daily
OR
Macrolide (if pneumococcal resistance is <25%)

YES → **Recommended empiric therapy**

Combination therapy of amoxicillin/clavulanate **or** cephalosporin^ + macrolide
OR
Combination therapy of amoxicillin/clavulanate **or** cephalosporin + doxycycline
OR
Monotherapy with respiratory fluoroquinolone†

^ *cefpodoxime or cefuroxime*

Outpatient Treatment Strategies** are for adults with no risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa

* Risk factors include prior isolation of MRSA or *P. aeruginosa* from the respiratory tract in the last 12 months or hospitalization **AND** receipt of parental antibiotics in the last 90 days

Key Points

- Obtain a MRSA nasal PCR to identify patients that require MRSA coverage *(and those that do not)*
- 5 days of antibiotic therapy is recommended for patients with an appropriate initial response to therapy and who are clinically stable
- Antibiotic therapy for CAP due to *Staphylococcus aureus* or *Pseudomonas aeruginosa* should be continued for at least 7 days in patients with an appropriate initial response to therapy
- Testing for influenza is recommended **if** it is prevalent in the community
- Testing for *Legionella* is recommended **if** indicated by epidemiological risk factors

Note: Assess for antibiotic allergies and use alternative agents as appropriate. Suggested antibiotic doses are for normal renal function; Adjust for renal impairment when necessary.

This is intended only as a guide for evidence-based decision-making. It is not intended to replace clinical judgment.

INPATIENT

Assess for severity of CAP

Severe CAP

Additional Diagnostic Studies

- *Legionella* antigen testing
- Pneumococcal urinary antigen
- Blood AND respiratory cultures prior to antibiotic therapy

Severe CAP with risk factors for MRSA or *P. aeruginosa*
OR
Non-Severe CAP with prior respiratory tract isolation of MRSA or *P. aeruginosa*

Type of risk factors for MRSA or *Pseudomonas aeruginosa*

Severe CAP with recent hospitalization AND IV antibiotic exposure:

Vancomycin **OR** linezolid
PLUS
Combination therapy with antipseudomonal beta-lactam + macrolide
OR
Combination therapy with antipseudomonal beta-lactam + respiratory fluoroquinolone†

Severe or Non-Severe CAP with prior respiratory isolation of *Pseudomonas aeruginosa:*

Combination therapy with antipseudomonal beta-lactam + macrolide
OR
Combination therapy with antipseudomonal beta-lactam + respiratory fluoroquinolone†

Severe or Non-Severe CAP with prior respiratory isolation of MRSA:

Add vancomycin **OR** linezolid to standard CAP therapy

Prior respiratory tract isolation

CAP severity

Severe CAP
MRSA and *Pseudomonas* NOT isolated

Recommended therapy for Severe CAP

Combination therapy with beta-lactam + macrolide *
OR
Combination therapy with beta-lactam + respiratory fluoroquinolone† *
(*If neither macrolide or fluoroquinolone can be used, doxycycline can be substituted)

Change therapy based on culture results, if needed

Non-Severe CAP

Prior isolation of MRSA **AND/OR** *Pseudomonas aeruginosa* from the respiratory tract within 1 year

YES

NO

Hospitalization **AND** exposure to IV antibiotics within 90 days

YES

NO

Obtain blood **AND** respiratory cultures **prior** to antibiotic therapy
(if not previously obtained)

Non-Severe CAP ONLY with recent hospitalization and IV antibiotic exposure as a risk factor

Recommended empiric therapy for Non-Severe CAP

Combination therapy with a beta-lactam + macrolide
OR
Monotherapy with respiratory fluoroquinolone†
OR
Combination therapy with beta-lactam + doxycycline (*If macrolide and fluoroquinolone are contraindicated*)

Non-Severe CAP
MRSA and *Pseudomonas* NOT isolated

Change therapy based on culture results, if needed

APPROPRIATE clinical response

- Tolerating oral intake
- Normal mental status or at baseline
- Resolution of vital sign abnormalities (no tachycardia, no tachypnea, hemodynamically stable, supplemental oxygen needs improving or at baseline, afebrile)

APPROPRIATE clinical response

Transition to oral antibiotics and discharge as soon as all clinical stability criteria is met

Clinical WORSENING or INADEQUATE response

Consider the following:

- Wrong diagnosis or concomitant non-infectious disease
- Parapneumonic effusion, empyema or lung abscess
- Nosocomial superinfection
- Exacerbation of comorbid illness
- Drug fever

† moxifloxacin, levofloxacin or delafloxacin *(please note - the use of delafloxacin was not addressed in this guideline as it was not indicated for community-acquired bacterial pneumonia at the time it was published; it is currently FDA-approved)*

Empiric Management of Hospital-Acquired Pneumonia (HAP) in Non-Pregnant Adults

Pneumonia develops ≥ 48 hours following hospitalization

Is the patient at a high risk for mortality?
(e.g., need for ventilator support due to HAP or septic shock)
OR
Has the patient been exposed to IV antibiotics in the last 90 days?

NO

Colonization or prior infection with MRSA?
OR
Is the local prevalence of MRSA **>**20% or not known?

YES

Add MRSA coverage
(e.g., vancomycin, linezolid)
Do not use daptomycin

NO

Does the patient have structural lung disease?

NO

Single anti-pseudomonal coverage

Beta-Lactams^	Fluoroquinolones
Cefepime Ceftazidime Piperacillin/tazobactam Imipenem Meropenem Aztreonam	Levofloxacin Ciprofloxacin

YES

MRSA coverage
(e.g., vancomycin, linezolid; do not use daptomycin)
PLUS
Double anti-pseudomonal coverage†
with two antibiotics from different classes

Beta-Lactams^	Fluoroquinolones	Aminoglycosides*
Cefepime Ceftazidime Piperacillin/tazobactam Imipenem Meropenem Aztreonam	Levofloxacin Ciprofloxacin	Tobramycin

YES

Double anti-pseudomonal coverage†
with two antibiotics of different classes

Beta-Lactams^	Fluoroquinolones	Aminoglycosides*
Cefepime Ceftazidime Piperacillin/tazobactam Imipenem Meropenem Aztreonam	Levofloxacin Ciprofloxacin	Tobramycin

† Individual ICUs may choose to customize their criteria for using two anti-pseudomonal agents. Review patient microbiology history and consult local/ institutional antibiograms when selecting antimicrobial therapy.

Key Points

- After 48-72 hours, assess if the patient is responding clinically, evaluate culture data, and tailor therapy to the identified pathogen.
- If no pathogen is identified, re-assess need for antibiotics and consider alternative non-infectious etiologies
- If patient is not improving clinically, assess for an alternative diagnosis, complication or fungal/viral pathogen
- 7 days of therapy is recommended for patients with an appropriate response and who are clinically improving or stable

Diagnostic Testing

- Blood cultures prior to antibiotics
- Respiratory specimen for culture prior to antibiotics
- Consider obtaining an MRSA nares PCR to rapidly determine if anti-MRSA antibiotics are indicated

^ While **ertapenem** is a carbapenem, it does **not** have coverage against *P. aeruginosa*. Anti-pseudomonal carbapenems (imipenem, meropenem) should be reserved for situations when other agents would not be appropriate.

***** Per the revised **aminoglycoside** breakpoints published by the CLSI, **gentamicin** is **no longer** considered to be a clinically effective treatment option for *P. aeruginosa* infections. Additionally, the CLSI update states that **amikacin** should only be considered as an option for **UTIs** caused by *P. aeruginosa*.

Note: This is intended only as a guide for evidence-based decision-making. It is not intended to replace clinical judgment.

Reference:
Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61-e111. doi:10.1093/cid/ciw353

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Empiric Management of Ventilator-Associated Pneumonia (VAP) in Non-Pregnant Adults

Pneumonia develops ≥ 48 hours following mechanical ventilation

Septic shock at the time of VAP?
OR
Has the patient been exposed to IV antibiotics in the past 90 days?
OR
Acute respiratory distress syndrome preceding VAP?
OR
Acute renal replacement therapy prior to VAP?
OR
Five or more days of hospitalization prior to VAP?

YES

NO

Colonization or prior infection with MRSA?
OR
Is the local prevalence of MRSA >10-20% or not known?

YES

NO

Add MRSA coverage
(e.g., vancomycin, linezolid)
Do not use daptomycin

Is the local prevalence of Gram-negative isolates resistant to an antibiotic being considered for monotherapy >10%?
OR
Are the local antimicrobial susceptibility rates for Gram-negative bacilli not known?

NO

Single anti-pseudomonal coverage

Beta-Lactams^	Fluoroquinolones
Cefepime Ceftazidime Piperacillin/tazobactam Imipenem Meropenem Aztreonam	Levofloxacin Ciprofloxacin

YES

MRSA coverage *(e.g., vancomycin, linezolid; do not use daptomycin)*
PLUS
Double anti-pseudomonal coverage with two antibiotics from different classes†
(avoid two concurrent beta-lactams and do not combine aminoglycosides with polymyxins)

Beta-Lactams^	Fluoroquinolones	Aminoglycosides*	Polymyxins**
Cefepime Ceftazidime Piperacillin/tazobactam Imipenem Meropenem Aztreonam	Levofloxacin Ciprofloxacin	Tobramycin	Polymyxin B Colistin

Double anti-pseudomonal coverage† with two antibiotics of different classes

Beta-Lactams^	Fluoroquinolones	Aminoglycosides
Cefepime Ceftazidime Piperacillin/tazobactam Imipenem Meropenem Aztreonam	Levofloxacin Ciprofloxacin	Tobramycin

Key Points

- After 48-72 hours, assess if the patient is responding clinically, evaluate culture data, and tailor therapy to the identified pathogen.
- If no pathogen is identified, re-assess need for antibiotics and consider alternative non-infectious etiologies
- If patient is not improving clinically, assess for an alternative diagnosis, complication or fungal/viral pathogen
- 7 days of therapy is recommended for patients with an appropriate response and who are clinically improving or stable

Diagnostic Testing

- Blood cultures prior to antibiotics
- Respiratory specimen for culture prior to antibiotics
- Consider obtaining an MRSA nares PCR to rapidly determine if anti-MRSA antibiotics are indicated

**Polymyxins should be reserved for settings where there is a high prevalence of multidrug-resistance and there is local expertise available using this antibiotic class. Newer antimicrobials *(including but not limited to)* delafloxacin, ceftazidime-avibactam, ceftolozane-tazobactam and cefiderocol were not FDA-approved for use in VAP at the time this guideline was published. If possible, newer antimicrobials should be considered instead of polymyxins due to improved safety.

† Individual ICUs may choose to customize their criteria for using two anti-pseudomonal agents. Review patient microbiology history and consult local/institutional antibiograms when selecting antimicrobial therapy.

^While **ertapenem** is a carbapenem, it does **not** have coverage against *P. aeruginosa*. Anti-pseudomonal carbapenems (imipenem, meropenem) should be reserved for situations when other agents would not be appropriate.

***** Per the revised **aminoglycoside** breakpoints published by the CLSI, **gentamicin** is **no longer** considered to be a clinically effective treatment option for *P. aeruginosa* infections. Additionally, the CLSI update states that **amikacin** should only be considered as an option for **UTIs** caused by *P. aeruginosa*.

Note: This is intended only as a guide for evidence-based decision-making. It is not intended to replace clinical judgment.

Reference:
Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61-e111. doi:10.1093/cid/ciw353

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CDC Sexually Transmitted Infections Treatment Guidelines (2021)

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*Summary of Recommended Therapies in Adult Patients**

**Does not address special populations such as pregnant patients, pediatric patients, or patients with HIV*

Acute Epididymitis

Ceftriaxone 500 mg IM x 1 dose, *plus*
Doxycycline 100 mg PO BID x 10 days
(for likely chlamydial/gonococcal infection)

Bacterial Vaginosis

Metronidazole 500 mg PO BID x 7 days

Cervicitis

Doxycycline 100 mg PO BID x 7 days
(empiric therapy for high-risk patients)

Chancroid

Azithromycin 1000 mg PO x 1 dose
or
Ceftriaxone 250 mg IM x 1 dose

Chlamydia

Doxycycline 100 mg PO BID x 7 days

Genital Herpes

Valacyclovir 1000 mg PO BID
for 7 - 10 days
(initial episode)

Granuloma Inguinale

Azithromycin 1000 mg PO weekly
(or 500 mg daily) for > 3 weeks
(until all lesions have healed)

HPV Anogenital Warts

Imiquimod 5% cream:
Apply at bedtime 3 nights per week
for < 16 weeks

Lymphogranuloma Venereum

Doxycycline 100 mg PO BID x 21 days

Mycoplasma Genitalium

Doxycycline 100 mg PO BID x 7 days *then,*
Moxifloxacin 400 mg PO QD x 7 days
(empiric therapy for when resistance testing not available)

Pediculosis Pubis

Permethrin 1% cream rinse:
Apply to affected area and wash off
after 10 minutes

Pelvic Inflammatory Disease

Ceftriaxone 500 mg IM x 1 dose, *plus*
Doxycycline 100mg PO BID x 14 days, *plus*
Metronidazole 500 mg PO BID x 14 days
(outpatient therapy)

Proctitis

Ceftriaxone 500 mg IM x 1 dose
plus
Doxycycline 100 mg PO BID x 7 days

Scabies

Permethrin 5% cream:
Apply to all areas of body from neck
down and wash off after 8-14 hrs

Syphilis

Benzathine penicillin G (Bicillin L-A®)
2.4 million units IM x 1 dose
(primary & secondary stages)

Trichomoniasis

Females: **Metronidazole 500 mg**
PO BID x 7 days
Males: **Metronidazole 2 g PO x 1 dose**

Uncomplicated Gonorrhea

Ceftriaxone 500 mg IM x 1 dose

if chlamydia infection cannot be ruled out add doxycycline 100 mg PO BID x 7 days

Uncomplicated Vulvovaginal Candidiasis

OTC: **Miconazole 1200 mg**
vaginal suppository x 1 dose *or*
Rx: Fluconazole 150 mg PO x 1 dose

Urethritis

Doxycycline 100 mg PO BID x 7 days
(non-gonococcal)

Reference:
Workowski, K. A., Bachmann, L. H., Chan, P. A., Johnston, C. M., Muzny, C. A., Park, I., Reno, H., Zenilman, J. M., & Bolan, G. A. (2021). Sexually transmitted infections treatment guidelines, 2021. MMWR. Recommendations and Reports: Morbidity and Mortality Weekly Report. Recommendations and Reports, 70(4), 1-187.

Simplified Hepatitis C Treatment Summary

Based on the AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C *(including changes highlighted in the 2023 Update)*

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HCV Diagnosis and Treatment Candidates

Diagnosis of HCV Infection

HCV antibody test
↓
REACTIVE
↓
HCV RNA test
↓
DETECTED
↓
Current HCV infection

***Adapted from**: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18)*

Goals of Therapy

- **Reduce mortality**
- **Prevent liver-related health complications**
- **Achieve sustained virologic response (SVR)**
  - Undetectable HCV RNA for at least 12 weeks after treatment completion
  - Achieving SVR = **virological cure**

Who is Eligible for Simplified Treatment?

- **Treatment-naive adult** patients without cirrhosis or with compensated cirrhosis (Child-Pugh A) who do not belong in any of the special patient groups*
- **The <u>majority</u> of patients are eligible for simplified treatment***

*The following patients are ***<u>not eligible</u>*** for simplified treatment:

- Prior hepatitis C treatment *(i.e. treatment-experienced patients)*
- HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation
- Current or prior episode of decompensated cirrhosis *(Child-Turcotte-Pugh [CTP] score ≥7)*
- Cirrhosis **AND** end-stage renal disease *(eGFR < 30 mL/min/m2)*

Pre-treatment Assessment

Assess at any point prior to starting treatment

- Quantitative HCV RNA (IU/mL)
- HIV antigen/antibody
- HBV (HBsAg, anti-HBc, and anti-HBs)
- Pregnancy (serum testing)
- HCV genotype (if considering sofosbuvir/velpatasvir in a patient with cirrhosis)
- CTP score (if considering simplified treatment in a patient with cirrhosis)
- FIB-4 score
- Evidence of cirrhosis
  - Transient elastography, serologic tests, prior liver biopsy, or other clinical evidence of cirrhosis

Assess within 6 months prior to starting treatment

- Complete blood count (CBC)*
- Hepatic function panel*
- Estimated glomerular filtration rate (eGFR)*
- International normalized ratio (INR)*
- Liver ultrasound (if considering simplified treatment in an patient with cirrhosis)

**Test within 3 months prior to initiating (not within 6 months) if initiating simplified treatment in a patient with compensated cirrhosis.*

***CTP:** Child-Turcotte-Pugh*
***FIB-4:** Fibrosis-4*

Monitoring

- **No** routine **laboratory** monitoring required for most patients
- Monitor for **side effects** in all patients
- Monitor for **hypoglycemia** in patients taking **medications for glycemic control***
- Monitor for **subtherapeutic INR** in patients taking **warfarin***
- Monitor for liver injury / worsening liver tests in patients with **compensated cirrhosis**
- Assess HCV RNA (plus hepatic function in patients with cirrhosis) **<u>at least 12 weeks</u>** after treatment completion to confirm achievement of SVR

**Clearance of HCV infection may lead to changes in liver function, which may impact response to these medications*

Simplified Pangenotypic Treatment Options

Glecaprevir 100 mg / Pibrentasvir 40 mg (Mavyret)

Take **<u>3 tablets</u>** (**100 mg/40 mg x 3**) by mouth once daily **with food** for **8 weeks**

- Use with **ethinyl estradiol-containing medications** (such as combined oral contraceptives) is **not** recommended due to concerns for **ALT elevation**
- Coadministration with **statins** increases the risk for myopathy and rhabdomyolysis (fluvastatin, pravastatin, rosuvastatin, and pitavastatin may require dose adjustments; **avoid atorvastatin, lovastatin, simvastatin**)

<u>OR</u>

Sofosbuvir 400 mg / Velpatasvir 100 mg (Epclusa)

Take 1 tablet (400 mg/100 mg) by mouth once daily **with or without food** for **12 weeks**

- Test HCV genotype for patients with compensated cirrhosis; those with genotype 3 **without** NS5A resistance-associated substitution Y93H may receive 12 weeks of Epclusa
- Separate dosing from **acid-reducing agents**,
  - **Antacids:** separate from Epclusa by 4 hr
  - **H2RAs:** give simultaneously or separate from Epclusa by 12 hr; avoid doses higher than famotidine 40 mg BID (or equivalent)
  - **PPIs:** not recommended; if necessary, take Epclusa with food 4 hr before omeprazole 20 mg

Shared Counseling Points

- Store in the **original container**
- Avoid missing doses
- Common side effects are **headache** and **fatigue**
- Avoid excess alcohol use
- Risk of **HBV reactivation** in coinfected patients (during or after HCV treatment)
- **High risk for drug interactions**:
  - All direct-acting antivirals should be avoided with strong CYP3A4 inducers
  - Avoid amiodarone use with sofosbuvir-containing regimens

Check with healthcare provider before starting new meds, supplements and herbal products

Follow Up

If SVR was achieved

- No liver-related follow-up needed in patients without cirrhosis
- **Patients with cirrhosis:** monitor (ultrasound) for hepatocellular carcinoma every 6 months **AND** monitor (endoscopic surveillance*) for esophageal varices

  **Follow the AASLD's portal hypertensive bleeding in cirrhosis guidelines*
- If the patient is at **ongoing risk for HCV infection** *(e.g., IV drug use, MSM engaging in unprotected sex)* test HCV RNA **annually**

If SVR was NOT achieved

- **Refer to specialist** for evaluation for **retreatment**
- Assess for disease progression **every 6-12 months** until retreatment begins
- **Patients with cirrhosis:** ultrasound **every 6 months** for hepatocellular carcinoma

Reference: [1] The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated October 2022.
[2] Bhattacharya D, Aronsohn A, Price J, et al. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clinical Infectious Diseases. 2023:ciad319. doi:10.1093/cid/ciad319

Cirrhosis Pharmacotherapy Summary

Based on the AFP guideline on cirrhosis (2019), AASLD guidelines on portal hypertensive bleeding (2016) and ascites/SBP/HRS (2021), and AASLD/EASL guideline on hepatic encephalopathy (2014)

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Overview of Cirrhosis

What is cirrhosis?

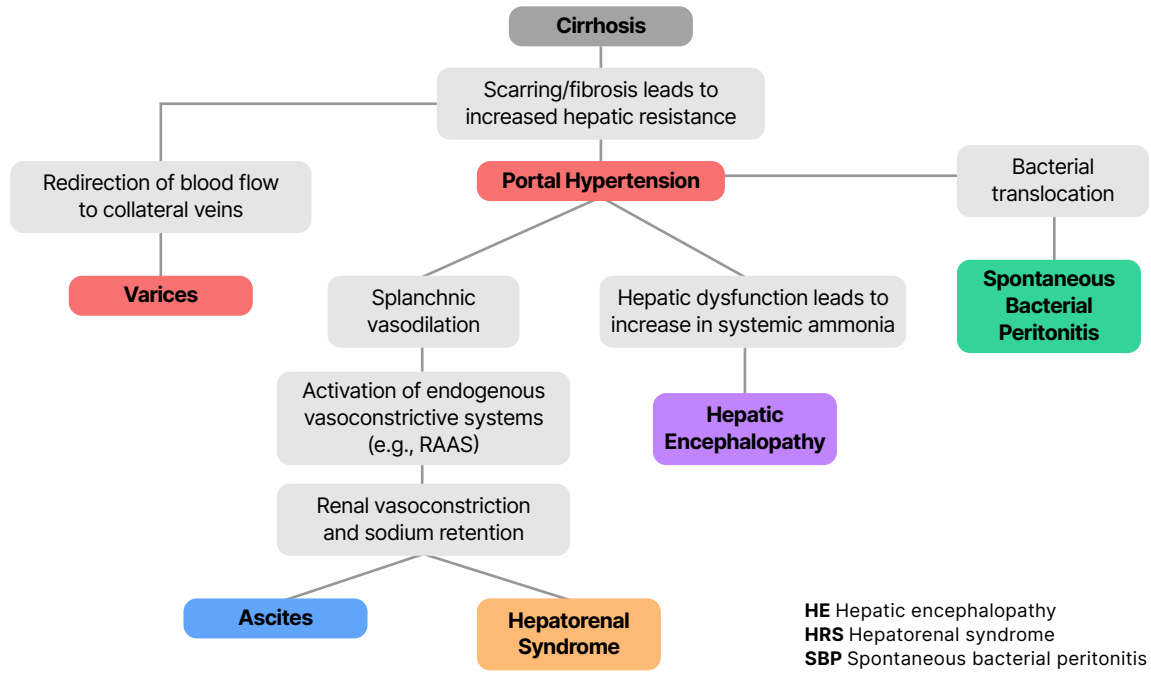
- **End-stage** of chronic liver disease
- Characterized by **advanced fibrosis/scarring**
- Complications include portal hypertension, varices, ascites, HE, HRS, SBP, liver cancer, and liver failure
- Common causes: alcohol-associated liver disease, chronic viral hepatitis infection, nonalcoholic fatty liver disease
- Diagnosed by **liver biopsy** (gold standard but invasive) or clinical findings (imaging, labs, medical history, presentations)

Classification of cirrhosis

- Child-Turcotte-Pugh (**CTP**) or Child-Pugh (**CP**) score assesses stage and severity of cirrhosis
  - Considers total bilirubin, albumin, INR, and degree of ascites and encephalopathy
  - Classifies into A (compensated), B (early decompensated), or C (severely decompensated)
- Model for End-Stage Liver Disease (**MELD**)score assesses prognosis (3-month mortality) for patients with cirrhosis
  - 12 or higher predicts increased risk of complications

Goals of therapy

- Prevent complications of cirrhosis
- Prevent hepatic decompensation
- Reduce mortality



HE Hepatic encephalopathy
HRS Hepatorenal syndrome
SBP Spontaneous bacterial peritonitis

Portal Hypertension (PH) & Varices

- Scarring of liver impedes blood flow through portal vein, increasing the blood pressure
  - **Varices** = distension in collateral vessels from redirected blood; at risk of **variceal hemorrhage**
- PH defined as **hepatic venous pressure gradient (HVPG) > 5 mmHg**
  - HVPG = difference in pressure between portal vein and hepatic veins
  - HVPG ≥ 10 mmHg = **clinically significant portal hypertension (CSPH)**
- **Primary prophylaxis of variceal hemorrhage**
  - A beta-blocker (**propranolol** 20-40 mg twice daily, **nadolol** 20-40 mg once daily, or **carvedilol** 6.25 mg twice daily) continued indefinitely, **OR**
  - Endoscopic variceal ligation (**EVL**) every 2-8 weeks until variceal eradication
- **Treatment of acute variceal hemorrhage**
  - **IV ceftriaxone (**1 g/day x max 7 days) + **EVL** + a vasoactive drug (see below)
    - **Octreotide**: 50 mcg bolus → continuous infusion at 50 mcg/hr for 2-5 days, **or**
    - **Vasopressin**: continuous infusion at 0.2-0.4 units/min (max 0.8 units/min) for 24 hours + concurrent IV nitroglycerin to maintain SBP of 90 mmHg, **or**
    - **Terlipressin**: 2 mg IV every 4 hours during the first 48 hours to control bleeding, then 1 mg every 4 hours to prevent rebleeding (total duration 2-5 days)
- **Secondary prophylaxis of variceal hemorrhage**
  - A non-selective beta-blocker (**propranolol** 20-40 mg twice daily or **nadolol** 20-40 mg once daily) continued indefinitely, **AND**
  - **EVL** every 1-4 weeks until variceal eradication

Ascites

- Accumulation of **excess fluid** in the abdomen; often the first decompensating event
- **Dietary sodium restriction (to 2 g/day)** recommended for net fluid loss
- **Diuretic therapy (aldosterone antagonist + loop diuretic)**
  - **Preferred**: spironolactone + furosemide
  - Initially **spironolactone 100 mg + furosemide 40 mg per day**
  - Titrate to maximum of spironolactone 400 mg + furosemide 160 mg per day
  - At least **72-hour interval** needed between dose titrations
  - Taper down to the lowest effective dose after fluid is adequately mobilized
- Monitor daily body weight to assess efficacy of diuretics
  - Up to **0.5 kg/day weight loss** is generally appropriate (up to 1 kg/day for those with edema)

Spontaneous Bacterial Peritonitis (SBP)

- Often no clear source of infection; mainly Gram-negative bacteria (*E. coli*, *K. pneumoniae*) but some Gram-positive organisms can be common (*S. aureus*, *E. faecalis*, *E., faecium*)
- **Diagnosis:** polymorphonuclear (PMN) leukocyte > 250/mm3 in the ascitic fluid
- **Treatment: antibiotic therapy + IV albumin**
  - Empiric 3rd-gen cephalosporin (e.g., **ceftriaxone**, **cefotaxime**) generally recommended
  - **Broad spectrum** agents (e.g., **piperacillin/tazobactam**) recommended for healthcare-associated or nosocomial infection, those with recent exposure to broad-spectrum abx, or those admitted with sepsis/septic shock
  - Add **vancomycin** if prior MRSA infection or positive MRSA swab
  - Add **daptomycin** for vancomycin-resistant enterococcus
  - **Meropenem** +/- glycopeptide if current or recent exposure to piperacillin/tazobactam
  - Repeat diagnostic paracentesis **48 hours** from initiation; PMN decrease of **< 25%** from baseline may require broadening of antibiotic therapy or investigation of secondary peritonitis
- **Secondary prevention**
  - Long-term prophylaxis with **ciprofloxacin** 500 mg/day
- **Primary prevention**
  - IV ceftriaxone for patients with variceal hemorrhage (see PH & Varices section)
  - Generally only needed if high risk of infection present
  - **Ciprofloxacin** for patients with low ascitic fluid protein (< 1.5 g/dL) + and renal dysfunction or liver failure

Hepatorenal Syndrome (HRS)

- Renal complication due to hemodynamic changes and systemic inflammation associated with cirrhosis
- **Diagnosis of HRS-AKI (acute kidney injury from HRS)**
  - Cirrhosis with ascites
  - Diagnosis of AKI (↑ SCr by ≥ 0.3 mg/dL in 48 hr OR ≥ 50% ↑ in SCr in the past 7 days)
  - No response after 2 consecutive days of diuretic withdrawal & plasma volume expansion with albumin infusion
  - No current/recent use of nephrotoxic drugs, structural kidney injury, or shock
- **Treatment of HRS-AKI**
  - Vasoconstrictor (**terlipressin** preferred; **norepinephrine** also recommended) + **albumin**
  - Decrease in SCr to < 1.5 mg/dL or return to baseline within 0.3 mg/dL over maximum of **14 days** indicates **successful response**

Hepatic Encephalopathy (HE)

- Believed to be due to ammonia accumulation caused by hepatic dysfunction
- **Symptoms:** impaired memory and motor function, **asterixis ("flapping tremor")**, personality changes, coma
- Categorized with West Haven criteria (WHC grades 1 to 4)
- Diagnosed by excluding other causes of cognitive dysfunction
- **Short-term** protein restriction may be necessary for nitrogen modulation
- Treatment recommended for fully symptomatic overt HE
  - **Lactulose** (nonabsorbable disaccharide): preferred treatment
    - 30-45 mL every 1-2 hours until at least 2 soft stools/day are produced
    - Thereafter, titrated to maintain 2-3 soft stools/day
  - **Rifaximin** (add-on to lactulose) to **prevent** HE recurrence after **second** episode
    - 550 mg twice daily

Reference:
[1] American Association for the Study of Liver Diseases; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol. 2014 Sep;61(3):642-59. doi: 10.1016/j.jhep.2014.05.042. Epub 2014 Jul 8. Erratum in: J Hepatol. 2015 Oct;63(4):1055.
[2] Biggins SW, Angeli P, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 Practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021 Aug;74(2):1014-1048. doi: 10.1002/hep.31884.
[3] Garcia-Tsao G, Abraldes JG, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017 Jan;65(1):310-335. doi: 10.1002/hep.28906. Epub 2016 Dec 1. Erratum in: Hepatology. 2017 Jul;66(1):304.
[4] Smith A, Baumgartner K, et al. Cirrhosis: Diagnosis and management. Am Fam Physician. 2019;100(12):759-770.

Migraine Pharmacotherapy

Based on the American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice (2021)

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Acute Treatment

Acute Treatment Goals

- Achieve fast relief and freedom from symptoms
- Achieve functional recovery
- Minimize need for additional doses or medications
- Optimize of self-care and reduce need for resources
- Minimize adverse events
- Maintain cost-effective management

Important Considerations

- Individualized **lifestyle modifications** are important
- Acute treatment should be offered to **all patients** with confirmed migraine diagnosis
- Use acute treatment medications at the onset of attack, **at the first sign of pain**

Acute Treatment Options

Migraine-specific Agents

Established efficacy	Probably effective
• **Triptans** *(e.g., sumatriptan, rizatriptan, zolmitriptan)* • Ergotamine derivatives *(e.g., **dihydroergotamine**)* • Small molecule CGRP receptor antagonists *("**gepants**"; e.g., rimegepant, ubrogepant, zavegepant)* • Selective serotonin receptor agonist *(e.g., **lasmiditan**)*	• Ergotamine • Other forms of dihydroergotamine

Non-specific Agents

Established efficacy	Probably effective
• **NSAIDs** (*aspirin, diclofenac, ibuprofen, naproxen, celecoxib oral solution*) • Combination analgesic: ***(acetaminophen/aspirin/caffeine)***	• NSAIDs *(flurbiprofen, ketoprofen, IV or IM ketorolac)* • IV magnesium *(in migraine with aura)* • Isometheptene-containing compounds • Antiemetics *(chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine)*

Acute Treatment Recommendations

Mild to moderate attacks
Non-specific agents recommended

↓

Inadequate response to non-specific agents

→ **Triptan***

↓

Inadequate response to initial treatment

← **Second triptan**

↓

Criteria for initiating small molecule CGRP receptor antagonists, lasmiditan, or neuromodulatory devices

- Prescribed/recommended by a licensed clinician for an adult patient
- ICHD-3 diagnosis of migraine (with aura, without aura, or chronic)
- Either of the following regarding triptans:
  (1) Triptans are either contraindicated or not tolerated
  (2) Inadequate response to at least **two** oral triptans (per clinician's attestation or patient-reported outcome questionnaire)

↓

Small molecule CGRP receptor antagonists, lasmiditan, or neuromodulatory devices

Moderate to severe attacks
Migraine-specific agents recommended

↓

Triptan*

*Triptans are generally considered the first-line migraine-specific options; non-oral options such as dihydroergotamine may be considered for patients for whom traditional oral options are inappropriate (e.g., those with severe nausea/vomiting)

Preventive Treatment

Preventive Treatment Goals

- Reduce attack frequency, severity, and duration
- Reduce disability associated with migraine attacks
- Improve treatment response, prevent escalation
- Improve function
- Reduce need for intolerable, ineffective, unwanted acute treatment
- Reduce overall cost of migraine treatment
- Provide sense of control; allow self-management
- Improve health-related quality of life
- Reduce psychological burdens of migraine

When to Consider Preventive Treatment

Consider preventive treatment in **any** of these situations

- Significant interference in daily life from migraine attacks despite acute treatment
- **Frequent attacks****
- Contraindication to acute treatments or failure of acute treatments
- Adverse effects associated with acute treatment
- **Overuse**** of acute treatments
- Patient preference
- Certain uncommon migraine types (e.g., brainstem or prolonged aura)
- History of migrainous infarction (regardless of attack frequency)

Preventive Treatment Options

Oral Agents

Established efficacy	Probably effective
• Candesartan • Antiepileptics *(divalproex sodium, valproate sodium, topiramate)* • Beta blockers *(metoprolol, propranolol, timolol)* • CGRP receptor antagonists *(rimegepant, atogepant)*	• Lisinopril • Antidepressants (amitriptyline, venlafaxine) • Beta blockers (atenolol, nadolol) • Memantine

Parenteral Agents

Established efficacy	Probably effective
• CGRP mAbs *(eptinezumab, erenumab, fremanezumab, galcanezumab)* • OnabotulinumtoxinA	• OnabotulinumtoxinA + CGRP mAb

**Definitions

Frequent attacks (for prevention criteria)

Offer preventive treatment if:
- ≥ 6 MHD, even if they cause no disability
- ≥ 4 MHD, if they cause some disability
- ≥ 3 MHD, if they cause severe disability

Consider preventive treatment if:
- 4 or 5 MHD with no disability
- 3 MHD with some disability
- 2 MHD with severe disability

Overuse (for prevention criteria)

- ≥ 10 days/month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused
- ≥ 15 days/month for nonopioid analgesics, acetaminophen, and NSAIDs

Adequate trials

- Oral agents: at least **8 weeks** at target therapeutic dose
  - Patients with partial response may experience additional benefit over 6-12 months
- Parenteral CGRP mAbs:
  - At least **3 months** (if administered monthly)
  - At least **6 months** (if administered quarterly)

Initiating CGRP mAbs

The guideline recommends that CGRP mAbs be considered for preventive treatment in a patient **18 years or older** if any of the three conditions to the right are met.

→

1. ICHD-3 diagnosis of migraine (with or without aura), **4-7 MMD**, and **both** of the following:
- Intolerability/inadequate response to an 8-week trial** of two or more of the preventive options listed above
- At least moderate disability

2. ICHD-3 diagnosis of migraine (with or without aura), **8-14 MMD** and intolerability/inadequate response to an 8-week trial** of two or more of the preventive options listed above

3. ICHD-3 diagnosis of **chronic** migraine and **either** of the following:
- Intolerability/inadequate response to an 8-week trial** of two or more of the preventive options listed above
- Intolerability or inadequate response to at least 2 quarterly injections of onabotulinumtoxinA

Reference: Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021;61(7):1021-1039. doi:10.1111/head.14153

Abbreviations

CGRP calcitonin gene-related peptide
ICHD-3 International Classification of Headache Disorders, 3rd edition
MHD monthly headache days
MMD monthly migraine days

NSAID Selectivity

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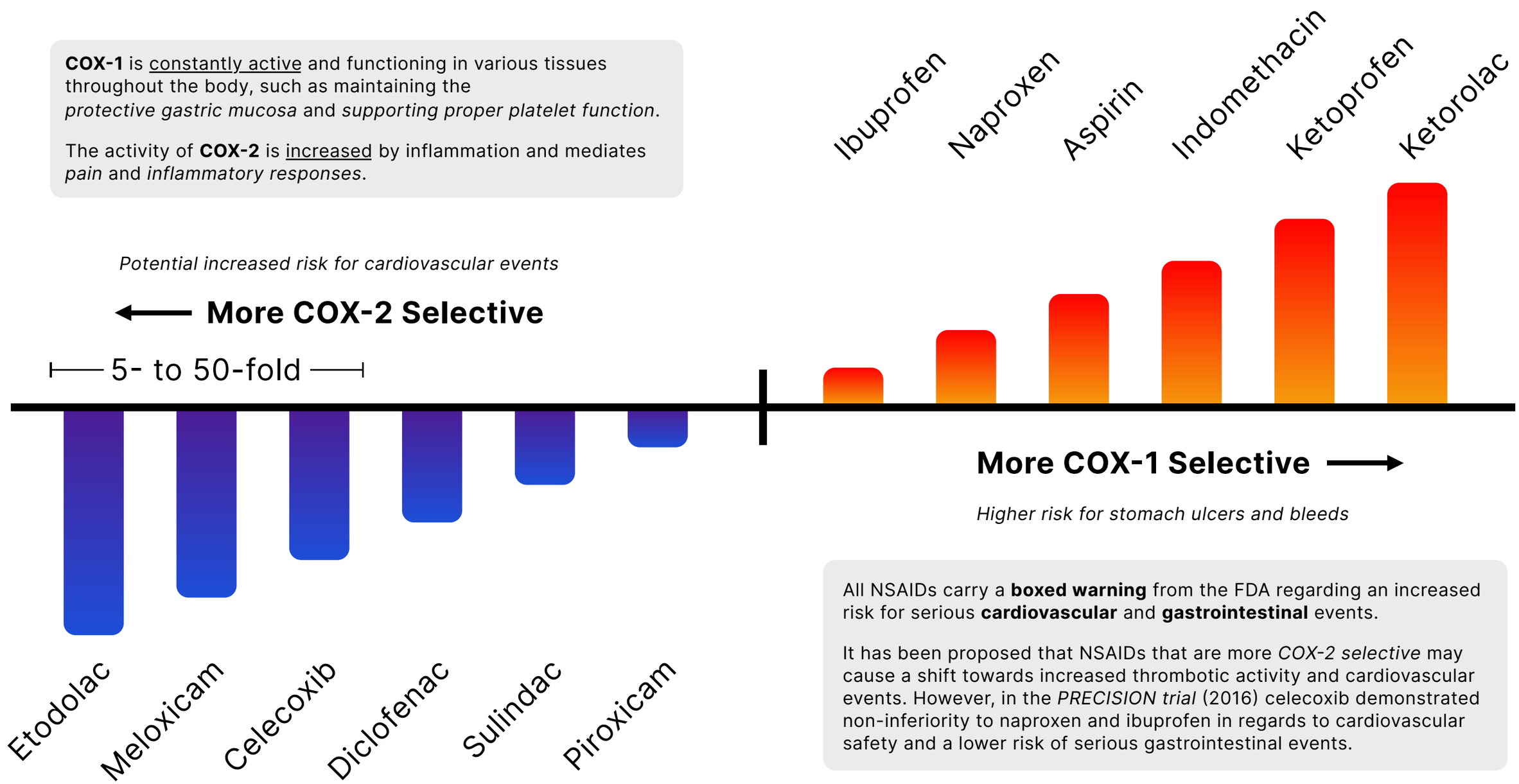
NSAIDs *(nonsteroidal anti-inflammatory drugs)* inhibit COX enzymes, **COX-1** and **COX-2**.

Different NSAIDs have varying degrees of **selectivity** for COX-1 and COX-2, which can influence their efficacy and side effect profiles.

Please note: not all NSAIDs are included in this chart.

COX-1 is constantly active and functioning in various tissues throughout the body, such as maintaining the *protective gastric mucosa* and *supporting proper platelet function*.

The activity of **COX-2** is increased by inflammation and mediates *pain* and *inflammatory responses*.



All NSAIDs carry a **boxed warning** from the FDA regarding an increased risk for serious **cardiovascular** and **gastrointestinal** events.

It has been proposed that NSAIDs that are more *COX-2 selective* may cause a shift towards increased thrombotic activity and cardiovascular events. However, in the *PRECISION trial* (2016) celecoxib demonstrated non-inferiority to naproxen and ibuprofen in regards to cardiovascular safety and a lower risk of serious gastrointestinal events.

References:

Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci U S A. 1999;96(13):7563-7568. doi:10.1073/pnas.96.13.7563

Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med. 2016;375(26):2519-2529.

Topical Corticosteroid Potencies

Table includes common preparations listed alphabetically in each group

Class 1 **Super Potent**	**Betamethasone dipropionate, augmented 0.05%** ointment (*Diprolene*), gel, lotion **Clobetasol propionate 0.05%:** lotion/shampoo/spray (*Clobex*), cream/ointment (*Temovate*), foam (*Olux*), gel **Desoximetasone 0.25%:** spray (*Topicort*) **Diflorasone diacetate 0.05%:** ointment (*Psorcon*) **Fluocinonide 0.1%:** cream (*Vanos*) **Flurandrenolide 4 mcg/sq. cm:** tape (*Cordran*) **Halobetasol propionate 0.05%:** cream, ointment, lotion (*Ultravate*), foam (Lexette)
Class 2 **High Potency**	**Amcinonide 0.1%:** ointment (*Amcort, Cyclocort*) **Betamethasone dipropionate 0.05%:** cream (*Diprolene AF*) **Clobetasol propionate 0.025%:** cream (*Impoyz*) **Desoximetasone 0.05%:** gel (*Topicort*), **0.25%:** cream/ointment (*Topicort*) **Diflorasone diacetate 0.05%:** cream (*Psorcon*), cream-emollient (*ApexiCon E*) **Fluocinonide 0.05%:** cream/gel/ointment/solution (*Lidex*) **Halcinonide 0.1%:** cream/ointment/solution (*Halog*) **Halobetasol propionate 0.01%:** lotion (*Bryhali*) **Mometasone furoate 0.1%:** ointment (*Elocon*)
Class 3 **High-Medium**	**Amcinonide 0.1%:** cream/lotion (*Amcort, Cyclocort*) **Betamethasone valerate 0.1%:** ointment (*Valisone*), **0.12%:** foam (*Luxiq*) **Desoximetasone 0.05%:** cream (*Topicort LP*) **Fluocinonide 0.05%:** cream-emollient (*Lidex-E*) **Fluticasone propionate 0.005%:** ointment (*Cutivate*) **Triamcinolone acetonide 0.5%:** cream/ointment (*Kenalog, Triderm, Aristocort HP*)
Class 4 **Medium**	**Betamethasone dipropionate 0.05%:** spray (*Sernivo*) **Clocortolone pivalate 0.1%:** cream (*Cloderm*) **Fluocinolone acetonide 0.025%:** ointment (*Synalar*) **Flurandrenolide 0.05%:** ointment (*Cordran*) **Hydrocortisone valerate 0.2%:** ointment (*Westcort*) **Mometasone furoate 0.1%:** cream/lotion/solution **Triamcinolone acetonide 0.1%:** cream/ointment/spray (*Kenalog, Triderm*)
Class 5 **Low-Medium**	**Betamethasone dipropionate 0.05%:** lotion (*Diprosone*) **Betamethasone valerate 0.1%:** cream (*Beta-Val, Valisone*) **Desonide 0.05%:** lotion (*DesOwen*) **Fluocinolone acetonide 0.025%:** cream (*Synalar*) **Flurandrenolide 0.05%:** cream, lotion (*Cordran*) **Fluticasone propionate 0.05%:** cream, lotion (*Cutivate*) **Hydrocortisone butyrate 0.1%:** cream/lotion/ointment/solution (*Locoid*) **Hydrocortisone probutate 0.1%:** cream (*Pandel*) **Hydrocortisone valerate 0.1%:** cream (*Westcort*) **Prednicarbate 0.1%:** cream-emollient, ointment (*Dermatop*) **Triamcinolone acetonide 0.025%:** ointment (*Kenalog*), **0.1%:** lotion (*Kenalog*)
Class 6 **Mild**	**Alclometasone dipropionate 0.05%:** cream/ointment (*Aclovate*) **Fluocinolone acetonide 0.01%:** cream, solution (*Synalar*), oil (*Derma-Smoothe*), shampoo (*Capex*) **Desonide 0.05%:** cream (*Tridesilon*), gel (*Desonate*), foam (*Verdeso*) **Triamcinolone acetonide 0.025%:** cream (*Kenalog*), lotion (*Aristocort*)
Class 7 **Least Potent**	**Hydrocortisone acetate/base 0.5%, 1%, 2.5%:** cream (*Cortizone, Cortaid, MiCort-HC*), lotion, ointment, gel

Nasal Corticosteroid Dosing For Allergic Rhinitis

NASAL STEROID	ADULT DOSING	PEDIATRIC DOSING
Beclomethasone Beconase AQ, Qnasl *Rx Only*	**Beconase AQ:** 1-2 inhalations (42 mcg/inh) in each nostril twice daily. **Qnasl:** 2 sprays (80 mcg/spray) in each nostril once daily.	**Beconase AQ:** Age 6-11 years: 1 inhalation (42 mcg/inh) in each nostril twice daily (168 mcg); If uncontrolled, may increase to 2 inhalation twice daily (336 mcg). **Qnasl:** Age 4-11 years: 1 spray (40 mcg) in each nostril once daily (80 mcg total/day).
Budesonide Rhinocort Allergy *OTC* Rhinocort Aqua (DSC) *Rx Only*	**OTC dosing:** 2 sprays (32 mcg/spray) in each nostril once daily; Reduce to 1 spray/nostril/day once symptoms improve. **Rx dosing:** 1-4 sprays (32 mcg/spray) in each nostril once daily; Use lowest effective dose.	**OTC dosing:** Age 6-11 years: 1-2 sprays (32 mcg/spray) in each nostril once daily; Reduce to 1 spray/nostril/day once symptoms improve.
Flunisolide Various brands *Rx Only*	2 sprays (25 mcg/spray) in each nostril twice daily; May increase to 2 sprays three times/day.	Age 6-14 years: 1 spray (25 mcg/spray) in each nostril three times daily, or 2 sprays in each nostril twice daily.
Fluticasone Flonase Allergy Flonase Sensimist *OTC* Flonase Veramyst *Rx Only*	**OTC dosing (Flonase Allergy, fluticasone prop.):** 2 sprays (50 mcg/spray) in each nostril once daily; After 1 week, use 1-2 sprays/nostril once daily. **OTC dosing (Flonase Sensimist, fluticasone fur.):** 2 sprays (27.5 mcg/spray) in each nostril once daily; After 1 week, use 1-2 sprays/nostril once daily. **Rx dosing (Flonase, fluticasone prop.):** 2 sprays (50 mcg/spray) in each nostril once daily or 1 spray twice daily; May reduce to 1 spray/nostril for maintenance therapy. **Rx dosing (Veramyst, fluticasone fur.):** 2 sprays (27.5 mcg/spray) in each nostril once daily; May reduce to 1 spray/nostril for maintenance therapy.	**OTC dosing (Flonase Allergy, fluticasone prop.):** Age 4-11 years: 1 spray (50 mcg/spray) in each nostril once daily. **OTC dosing (Flonase Sensimist, fluticasone fur.):** Age 2-11 years: 1 spray (27.5 mcg/spray) in each nostril once daily. **Rx dosing (Flonase, fluticasone prop.):** Age 4+ years: 1 spray (50 mcg/spray) in each nostril once daily; If uncontrolled, may increase to 2 sprays/nostril once daily; Reduce to 1 spray/nostril once symptoms improve. **Rx dosing (Veramyst, fluticasone fur.):** Age 2-11 years: 1 sprays (27.5 mcg/spray) in each nostril once daily; If uncontrolled, may increase to 2 sprays/nostril daily; Reduce to 1 spray/nostril once symptoms improve.
Mometasone Nasonex *Rx Only*	2 sprays (50 mcg/spray) in each nostril once daily.	Age 2-11 years: 1 spray (50 mcg/spray) in each nostril once daily.
Triamcinolone Nasacort *OTC*	2 sprays (55 mcg/spray) in each nostril once daily; Reduce to 1 spray/nostril/day once symptoms improve.	Age 6-11 years: 1 spray (55 mcg/spray) in each nostril once daily; If uncontrolled, increase to 2 sprays/nostril once daily; Reduce to 1 spray/nostril/day once symptoms improve. Age 2-5 years: 1 spray (55 mcg/spray) in each nostril once daily.

Systemic Corticosteroids Comparison

CLASS	DRUG	EQUIVALENT DOSE	MINERALOCORTICOID ACTIVITY	DURATION
Short-Acting Glucocorticoid	**Hydrocortisone**	**20 mg**	**1**	**8-12 hours**
	Cortisone	**25 mg**	**0.8**	
Intermediate-Acting Glucocorticoid	**Prednisone**	**5 mg**	**0.8**	**12-36 hours**
	Prednisolone	**5 mg**	**0.8**	
	Methylprednisolone	**4 mg**	**0.5**	
	Triamcinolone	**4 mg**	**0**	
Long-Acting Glucocorticoid	**Dexamethasone**	**0.75 mg**	**0**	**36-72 hours**
	Betamethasone	**0.6 mg**	**0**	
Mineralocorticoid	**Fludrocortisone**	**N/A**	**125**	**18-36 hours**